


## MEMORANDUM

DATE: March 29, 1999

TO: Tom Bell, Mohandas Bhat, Frank Hawkins, Ruth Neta, Joseph Weiss, Libby White

FROM: Barrett Fountos 

SUBJECT: Summary of the First Meeting of the U.S. Members of the Binational Advisory Group (BAG) for the US-Chernobyl Studies of Thyroid Cancer, March 8, 1999

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This memo is to summarize the first meeting of the U.S. component of the Advisory Group for the US-Chernobyl Studies of Thyroid Cancer, held on March 8, 1999, at the Holiday Inn Bethesda. Copies of the agenda and handouts are attached.

Dr. Ihor Masnyk, National Cancer Institute (NCI), Division of Cancer Epidemiology and Genetics (DCEG), chaired the meeting. The US members of the Advisory Group are:

Dr. David Becker, New York Hospital—Cornell Medical Center  
Dr. Fred Mettler, University of New Mexico Hospital  
Dr. Bruce Napier, Pacific Northwest National Laboratory  
Dr. Roy Shore, New York University Medical Center  
Dr. Carole Spencer, University of Southern California, LA Campus

Other participants included:

Dr. Gil Beebe, NCI/DCEG, Head, Chernobyl Research Unit  
Dr. André Bouville, NCI/DCEG  
Dr. Bertrand Brill, University of Massachusetts Medical Center, NCI Consultant  
Ms. Betsy Duane, NCI/DCEG  
Mr. Barrett Fountos, EH-63  
Dr. Geoffrey Howe, Columbia University, NCI Scientific and Technical Support Contractor  
Mr. Roberto Minutillo, NCI Administrative Officer  
Dr. Herman Mitchell, NCI Consultant  
Dr. Al Rabson, NCI Deputy Director  
Dr. Jacob Robbins, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NCI Consultant  
Dr. Elaine Ron, NCI/DCEG, Chief, Radiation Epidemiology Branch  
Mr. Paul Phelps, NCI Contractor, Note Taker  
Ms. Denise Stoneman, NCI Administrative Officer  
Dr. Jake Wechselberger, NCI/DCEG, Executive Secretary, Thyroid Studies BAG  
Dr. Shlomo Yaniv, Nuclear Regulatory Commission (NRC)  
Dr. Sheila Zahm, NCI/DCEG, Deputy Director

## I. Organizational Changes at NCI Affecting the Management Responsibility of the Chernobyl Studies

Dr. Rabson described the reorganization at NCI that affects the personnel involved in the conduct and management of the Chernobyl thyroid and leukemia studies. Originally, these studies were located in the Division of Cancer Etiology, under the direction of Dr. Bruce Wachholz. Next, they were moved to the Division of Cancer Biology (DCB; now extramural studies). On February 5, 1999, the studies were formally moved to DCEG (now intramural studies). Dr. Wachholz remained in DCB; Drs. Masnyk and Bouville were transferred to DCEG. They report to Elaine Ron, Chief, Radiation Epidemiology Branch, within which was formed the Chernobyl Research Unit, a matrixed group of individuals working on the Chernobyl studies. Dr. Beebe directs the Chernobyl Research Unit and is responsible for the scientific direction of the studies. Dr. Beebe reports to Dr. Elaine Ron who reports to the Division Director, Joseph Fraumeni. Dr. Masnyk continues as Project Officer and is responsible for the implementation of the studies. Ms. Betsy Duane has responsibility for the legislative and communication aspects of the studies. Mr. Roberto Minuttillo and Ms. Denise Stoneman are Administrative Officers responsible for financial and budget issues related to the studies.

## II. Chernobyl Oversight Panel Established to Monitor the Chernobyl Studies

As a result of last year's Senate investigation, Dr. Rabson announced that there will be greater hands on oversight at the Department of Health and Human Services level. Within NCI, the program will continue to be monitored by the National Cancer Advisory Board (NCAB) and the NCI Board of Scientific Counselors. In addition, DCEG has established the Chernobyl Oversight Panel, which reports to Dr. Fraumeni. The Oversight Panel is Chaired by Dr. Sheila Zahm, Deputy Director, DCEG, who plans to convene monthly meetings. Dr. Jonathan Samet, a member of the NCI Board of Scientific Counselors, has agreed to serve on the Oversight Panel.

The purpose of the Oversight Panel is to ensure that:

- The scope of the projects is appropriate;
- The aims are achievable;
- The science and administrative procedures are sound; and
- The project takes full advantage of the in-house expertise.

Dr. Klausner recently approved an increase in NCI's contribution to the Chernobyl studies for a total of \$1.8 million for fiscal year 1999. In addition, NIH offered management assistance to the project and NIH auditors are now conducting an audit of the funding.

### III. History of the Chernobyl Studies and Discussion of Changes to the Thyroid Study Protocols

Dr. Masnyk gave a summary of the history of the thyroid studies, including how DOE, NCI, and NRC became involved. Dr. Beebe followed with a technical discussion of changes to the thyroid study protocols which will be shared with the scientists in Belarus and Ukraine.

### IV. Update on the Status of the Thyroid Studies

While the Belarus thyroid cohort remained fixed at 15,000, the cohort size of the Ukraine thyroid study was reduced from 70,000 to between 30,000 and 40,000 who were less than 19 years old at the time of the accident.

The protocol for the Belarus thyroid study was signed in May 1994. As of October 1998, 2,100 individuals had been screened. This total increased to 3,508 as of February 23, 1999. Of these, 13 new cases of thyroid cancer were detected, plus 28 existing cases, for a total of 41 thyroid cancers diagnosed to date.

The protocol for the Ukraine thyroid study was signed in May 1995. Exams began in April, 1998. As of February 24, 1999, 1,900 individuals had been screened. Of these, 3 new cases of thyroid cancer were detected.

Meanwhile, in January 1999, the flow of equipment and supplies to both countries was interrupted when the Veteran's Administration National Acquisition Center unilaterally withdrew from its agreement with NCI to ship equipment and supplies to Belarus and Ukraine. Until a new organization can be identified, shipments of equipment and supplies are on hold.

Dr. Mettler questioned the apparent lack of progress of the studies and suggested the use of milestones and performance indicators. Dr. Beebe explained that pathology data are considered good. He said that two to three more years are needed to fully enroll each cohort; then an additional 20 more years are needed to complete the studies. I suggested that NCI staff and BAG members consider implementing performance indicators similar to the ones in place for the DOE-sponsored cataract study in Ukrainian liquidators. This suggestion was well received.

Dr. Howe stated that the team is moving toward more focused, integrated approach of science and data management. However, Dr. Beebe mentioned that one major setback occurred when data notebooks apparently were stolen from a locked safe in Minsk. It is unclear how this will impact the progress of the study.

Dr. Howe recommended that the Chernobyl Unit prepare formal reports to Dr. Rabson (acting on behalf of Dr. Richard Klausner, Director, NCI), which would be sent from Dr. Klausner to Dr. Harold Varmus, Director, NIH.

It was pointed out that the Environmental Protection Agency provided \$50,0000 for assessing the database of environmental concentrations of I<sup>131</sup> in Belarus.

## V. Purpose and Functions of the BAG

The purpose of the BAG is to strengthen the fabric of the thyroid studies both scientifically and methodologically. The BAG is responsible for:

- Responding to requests for advice from Project Directors;
- Recommending changes/modifications to research protocols;
- Reviewing budgets presented;
- Reviewing progress of the work;
- Advising on publication policy;
- Initiating own agenda topics and investigations;
- Determining its own operating rules and membership rotation order; and
- Advising on continuation or possible termination of projects.

There is no BAG for the leukemia study; results of the pilot study will be reviewed.

The BAG, at its discretion has the option of convening in a closed Executive Session. The BAG, meeting in closed Executive Session, elected Dr. Napier as its Chair.

Dr. Masnyk will leave for both countries the week of March 15 to prepare the Belarus and Ukraine BAG members for the meeting with US BAG members in mid-May.

It was agreed that for the May meeting, BAG members need to identify expectations and clarify expectations of the Belarus and Ukrainian investigators so as to be sure the reasons for going to Chernobyl.

## Attachments



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

March 2, 1999

**Advisory Committee Meeting on March 8, 1999**

Dear Participants:

Please find enclosed the following materials for next Monday's meeting:

- ▶ Agenda for the March 8<sup>th</sup> Meeting
- ▶ Names and Addresses of the Advisory Committee
- ▶ Manual of Operations (dated December, 1997)
- ▶ Quarterly Report from Ukraine
- ▶ Quarterly Report from Belarus
- ▶ Dr. Masnyk's letter to Prof. Tronko - Trip Report to Ukraine
- ▶ Trip Report to Belarus
- ▶ Draft Material on Present Status of Project in Ukraine
- ▶ Draft Material on Present Status of Project in Belarus
- ▶ Summary of Proposed Changes to the UkrAm Thyroid Study Protocol
- ▶ Summary of Proposed Changes to the BelAm Thyroid Study Protocol
- ▶ Historical Report of Chernobyl Project

Sincerely,

Sandy Coopersmith  
Secretary to the Chernobyl Research Unit  
Radiation Epidemiology Branch  
National Cancer Institute  
6120 Executive Blvd., EPS/7th Floor  
Bethesda, MD 20892-7238  
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# **DRAFT AGENDA**

## **Initial Meeting U.S. Members of Advisory Groups for U.S.-Chornobyl Studies of Thyroid Cancer**

**March 8, 1999**

**National Cancer Institute, Bethesda, Maryland**

- |                      |  |
|----------------------|--|
| <b>8:30 - 8:45</b>   | Welcome (Dr. Alan Rabson, Deputy Director, NCI)  |
| <b>8:45 - 9:00</b>   | Introduction and Recent Administrative Changes at NCI (Dr. Ihor Masnyk, Project Director and Meeting Chairman) |
| <b>9:00 - 9:15</b>   | Objectives of Meeting and How We Got Here (Dr. Masnyk)   |
| <b>9:15 - 12:00</b>  | Proposed Changes in Formal Research Protocol (Dr. Gil Beebe)   |
| <b>10:00 - 10:15</b> | Break  |
| <b>12:00 - 1:00</b>  | Lunch  |
| <b>1:00 - 4:00</b>   | Present Status of Work on Each Arm of Project (Dr. Beebe)  |
| <b>2:30 - 2:45</b>   | Break  |
| <b>4:00 - 4:30</b>   | Selection of U.S. Chairman   |
| <b>4:30 - 4:45</b>   | Preparations for Meetings (Dr. Masnyk)   |
|                      | – Minsk  |
|                      | – Kiev   |
| <b>4:45 - 5:00</b>   | Logistics for Travel (Travel Coordinator)  |
|                      | – Visas, airline reservations, hotel reservations, flight from Minsk to Kiev                                   |
| <b>5:00 - 5:10</b>   | Adjournment  |

**NOMINATIONS FOR  
U.S. MEMBERS OF BINATIONAL ADVISORY COMMITTEES**

**David Becker, M.D.**  
**Professor of Radiology and Medicine**  
**Director of Nuclear Medicine**  
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**Radiation Thyroid**  
**Endocrinology**  
**Nuclear Medicine**

**Fred A. Mettler, Jr., M.D., M.P.H.**  
**Professor and Chairman**  
**Dept. of Radiology and Nuclear Medicine**  
**University of New Mexico Hospital**  
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**Radiology**  
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**Nuclear Medicine**  
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**Dosimetry**  
**Dose Reconstruction**

**Roy E. Shore, Ph.D.**  
**Professor of Environmental Medicine**  
**New York University Medical Center**  
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**Carole Spencer, Ph.D., M.T.**  
**Clinical Research Center**  
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**LAC-USC Medical Center**  
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**EMAIL: cspencer@hsc.usc.edu**

**Clinical Laboratory**  
**0 Sciences**

## BINATIONAL ADVISORY GROUPS

### U.S.A.

(Serving on both Belarus and Ukraine Groups)

David Becker, M.D.

Fred A. Mettler, Jr., M. D.

Bruce Napier, Ph.D.

Roy E. Shore, Ph.D.

Carole Spencer, Ph.D., M. T.

### Belarus

Chistenko, G. N. - Epidemiology

Markvarde, M. M. - Rad. Diagnosis

Milyutin, G. Yu. - Radiobiology

Radyuk, K. A. - Endocrinology

Tarutin, G. Yu. - Oncology

### Ukraine

Bodnar, O. N., Endocrinology

Frolkis, V. V., Academician

Korkushko, O. V., Pathophysiol.

Porevoznikov, O. N. Rad. Dosimetry

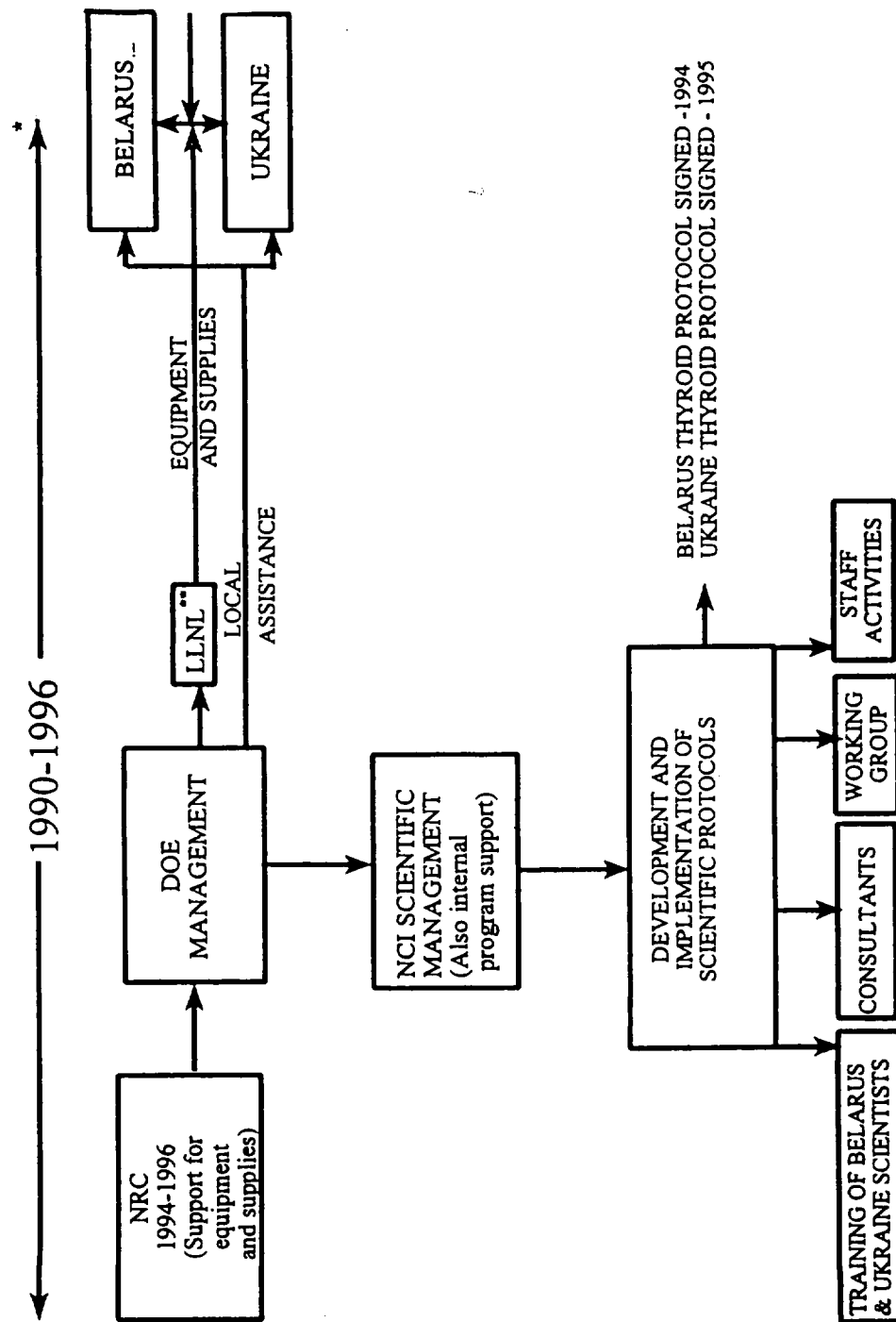
Prisyazhniuk, A. Ye. Epidemiology

# CHERNOBYL PROGRAM

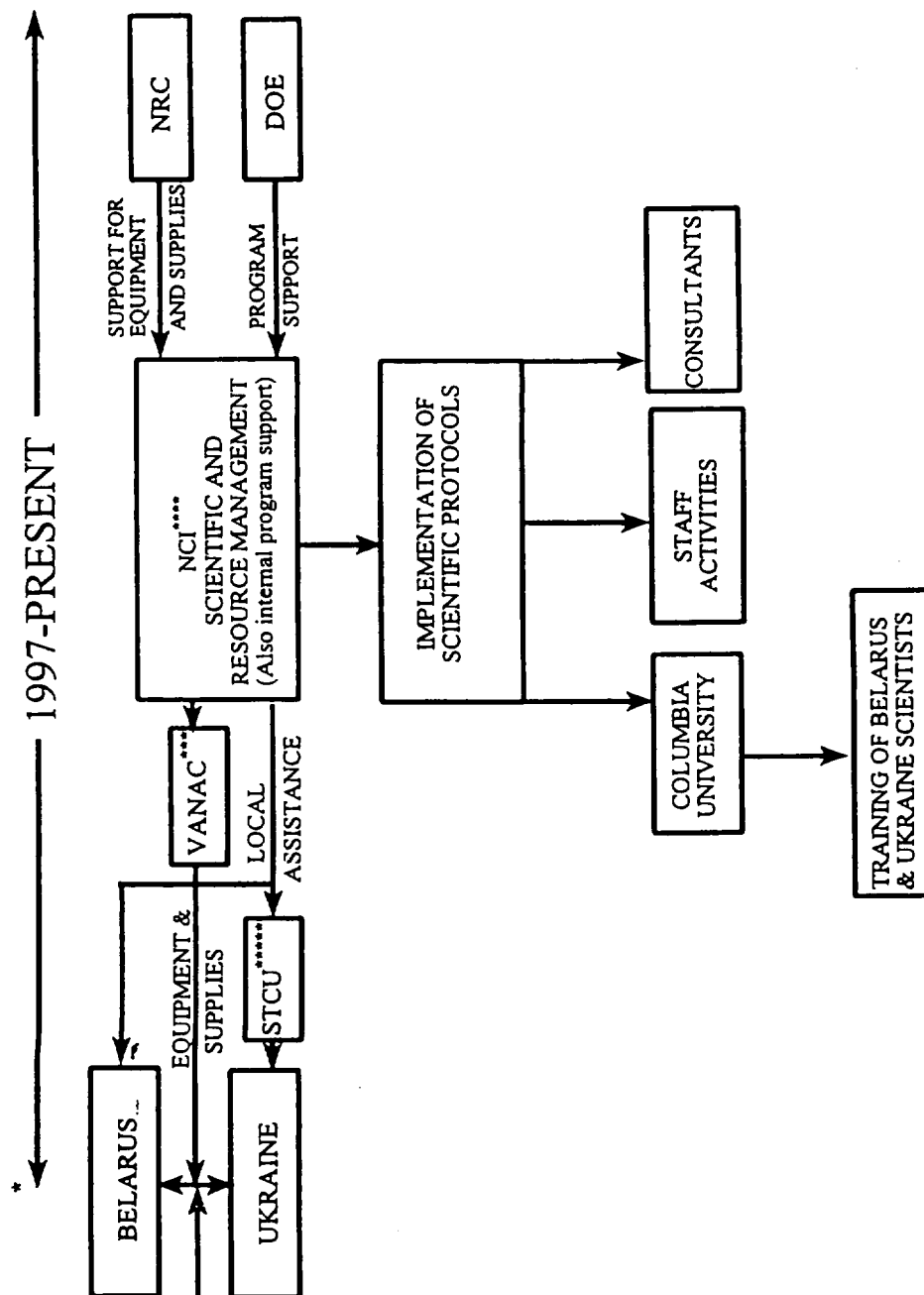
## BACKGROUND

- 1986: CHERNOBYL NUCLEAR POWER PLANT ACCIDENT
- 1987: PRESIDENTS REAGAN AND GORBACHEV
- 1988: JOINT COORDINATING COMMITTEE FOR CIVILIAN  
NUCLEAR REACTOR SAFETY
- 1989: DOE — HEALTH AND ENVIRONMENT
- 1990: NCI — THYROID AND LEUKEMIA STUDIES
- 1991-1996: DISSOLUTION OF USSR  
IDENTIFICATION OF ORGANIZATIONS/INDIVIDUALS  
DEVELOPMENT OF THREE RESEARCH PROTOCOLS
- PEER REVIEW
- IRB
- FINANCIAL SUPPORT: NCI, DOE, NRC
- 1996: NCI-DOE INTERAGENCY AGREEMENT  
FUNDING AGREEMENTS (UKRAINE AND BELARUS)
- 1996-1998: EQUIPMENT AND SUPPLIES  
IMPLEMENTATION

# INTERAGENCY COOPERATION AND RESOURCE MANAGEMENT FOR THYROID STUDIES IN BELARUS AND UKRAINE



# INTERAGENCY COOPERATION AND RESOURCE MANAGEMENT FOR THYROID STUDIES IN BELARUS AND UKRAINE



**Oversight/Overview**  
**Science, Budget, Management**

**HH&S**

**NIH Audit**

**NCAB**

**NCI Ececutive Committee**

**DCEG Board of Scientific Counselors**

**Chornobyl Oversight Panel**

**CHORNOBYL RESEARCH UNIT**

**Information/Reports**

**DOE**

**NRC**

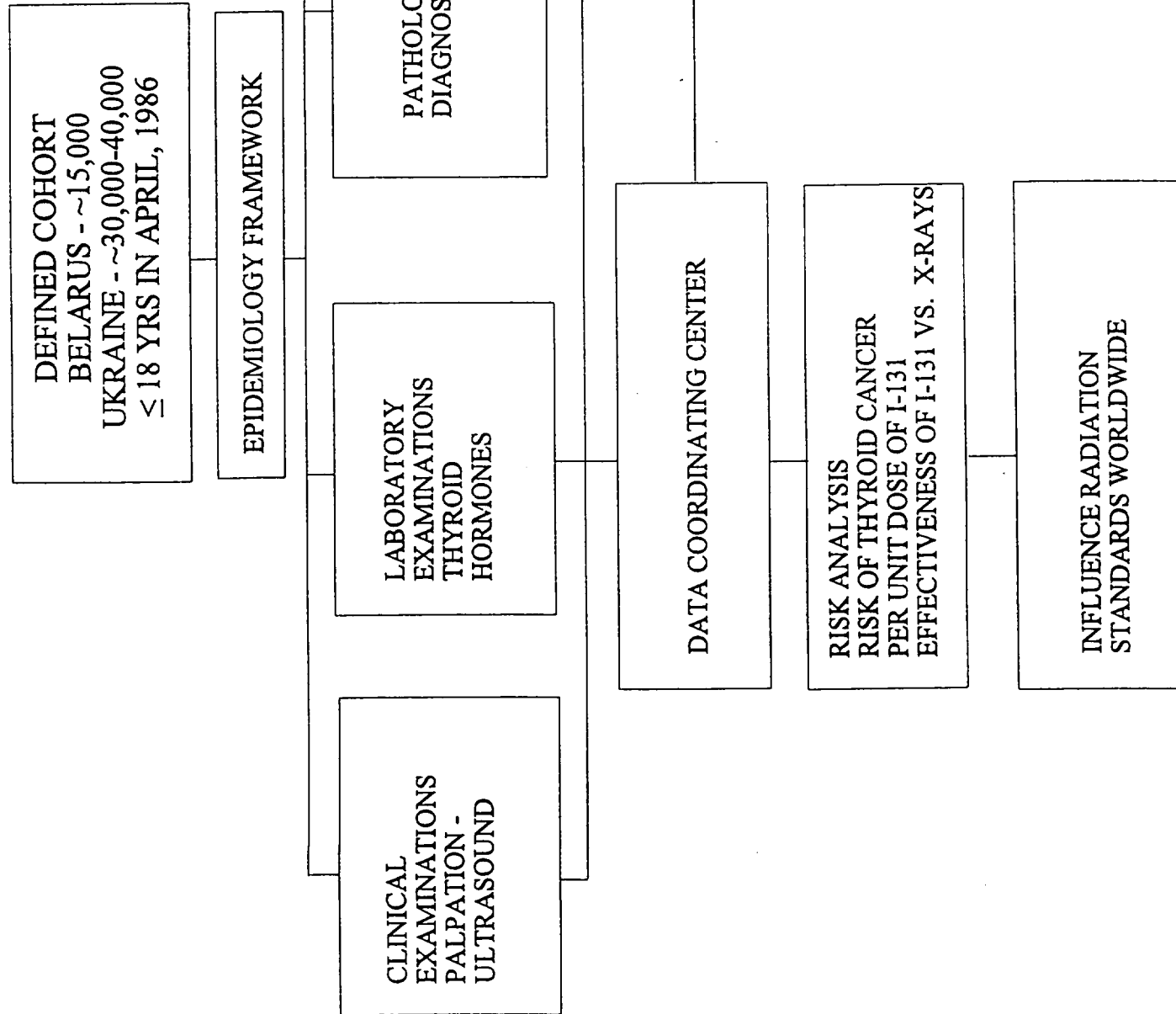
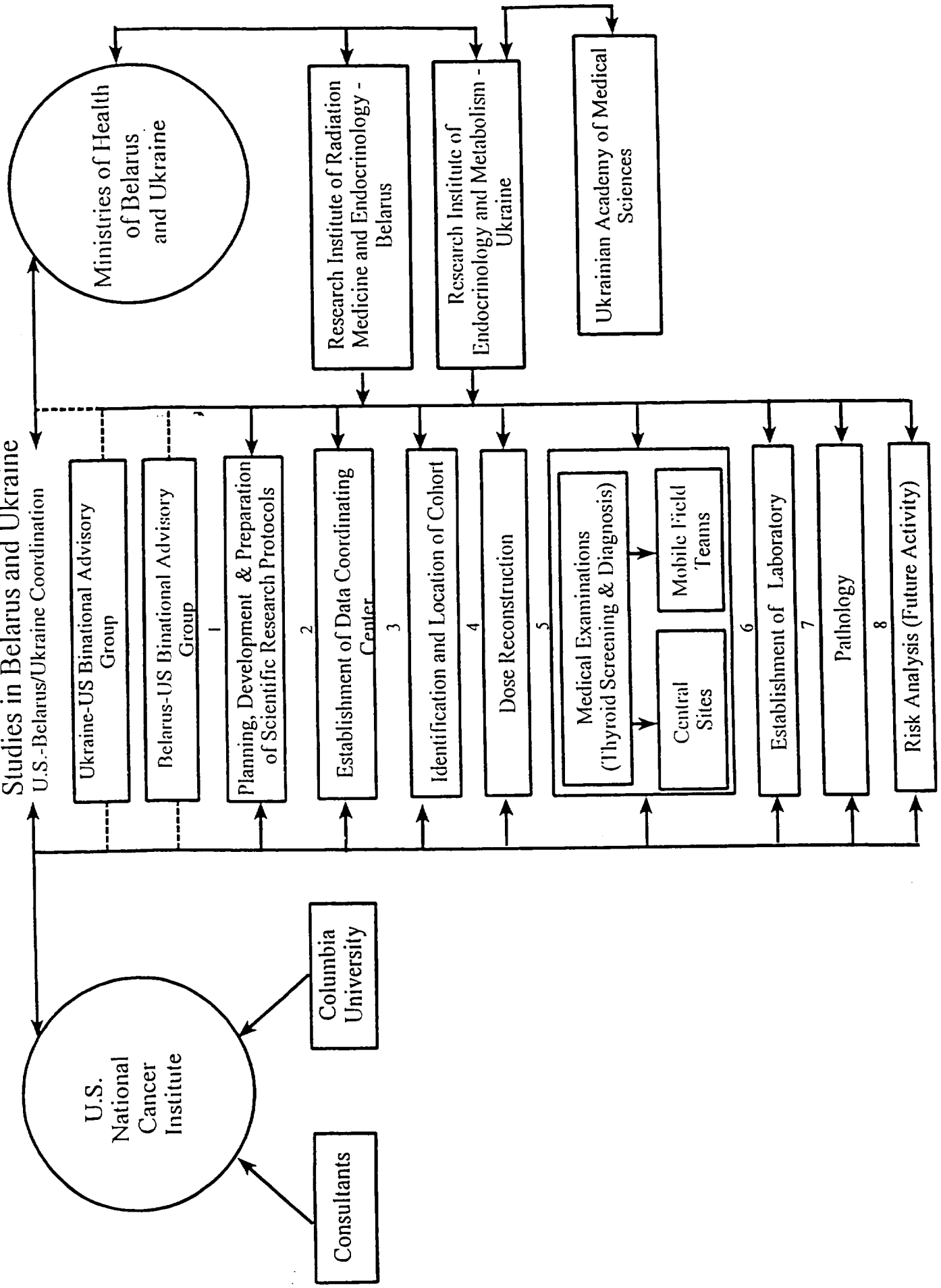


Figure 1  
Functional Implementation Schematic for Thyroid  
Studies in Belarus and Ukraine  
U.S.-Belarus/Ukraine Coordination



# UKRAINE

Ministry of Health

Academy of Medical Sciences of Ukraine

Science and Technology Center in Ukraine

Agency for Reconstruction and Development of Ukraine

Gluskov Institute of Cybernetics

Customs Officials

## Thyroid Project

Institute of Endocrinology and Metabolism

Cancer Register (Institute of Oncology)

Chief Physicians of Oblasts

Oblast Polyclinics

## NEW ORGANIZATION OF THE BELAM PROJECT

Ministry of Health

Scientific and Clinical  
Institute of Radiation  
Medicine and Endocrinology

Dispensary of  
Radiation Medicine  
Minsk

Specialized  
Dispensary of  
Radiation Medicine  
Gomel

Belorussian  
Center of  
Medical  
Technologies

Department of  
Radiation Protection  
of Hygiene Institute

Pathomorphology  
Department

Center of thyroid  
tumors

Clinic in Aksakovchina

## **INTERNATIONAL ORGANIZATIONS**

UNITED NATIONS  
WORD HEALTH ORGANIZATION  
INTERNATIONAL ATOMIC ENERGY AGENCY

EUROPEAN COMMISSION

## **U.S. DEPARTMENTS/AGENCIES**

DEPARTMENT OF STATE  
AMERICAN EMBASSY- BELARUS  
AMERICAN EMBASSY- UKRAINE

DEPARTMENT OF ENERGY

NUCLEAR REGULATORY COMMISSION

ENVIRONMENTAL PROTECTION AGENCY

DEPARTMENT OF VETERANS AFFAIRS

## **OTHER COUNTRIES**

JAPAN (SUSAKAWA FOUNDATION)

FRANCE (IPSN)

GERMANY (DFG)

USA (CONSORTIUM)

**BelAm Thyroid Project**

**Ministry of Health**

**Res. Inst. of Rad. Med.  
& Endocrinology**

**UkrAm Thyroid Project**

**Ministry of Health**

**Academy of Medical Sciences**

**Institute of Endocrinology  
& Metabolism**

**Res. Inst. of Rad. Medicine**

**BI-NATIONAL ADVISORY GROUP**

**ADVISORY TO:**

**BelAm Project Director:  
Ministry Staff**

**Deputy for Science:  
Institute Director**

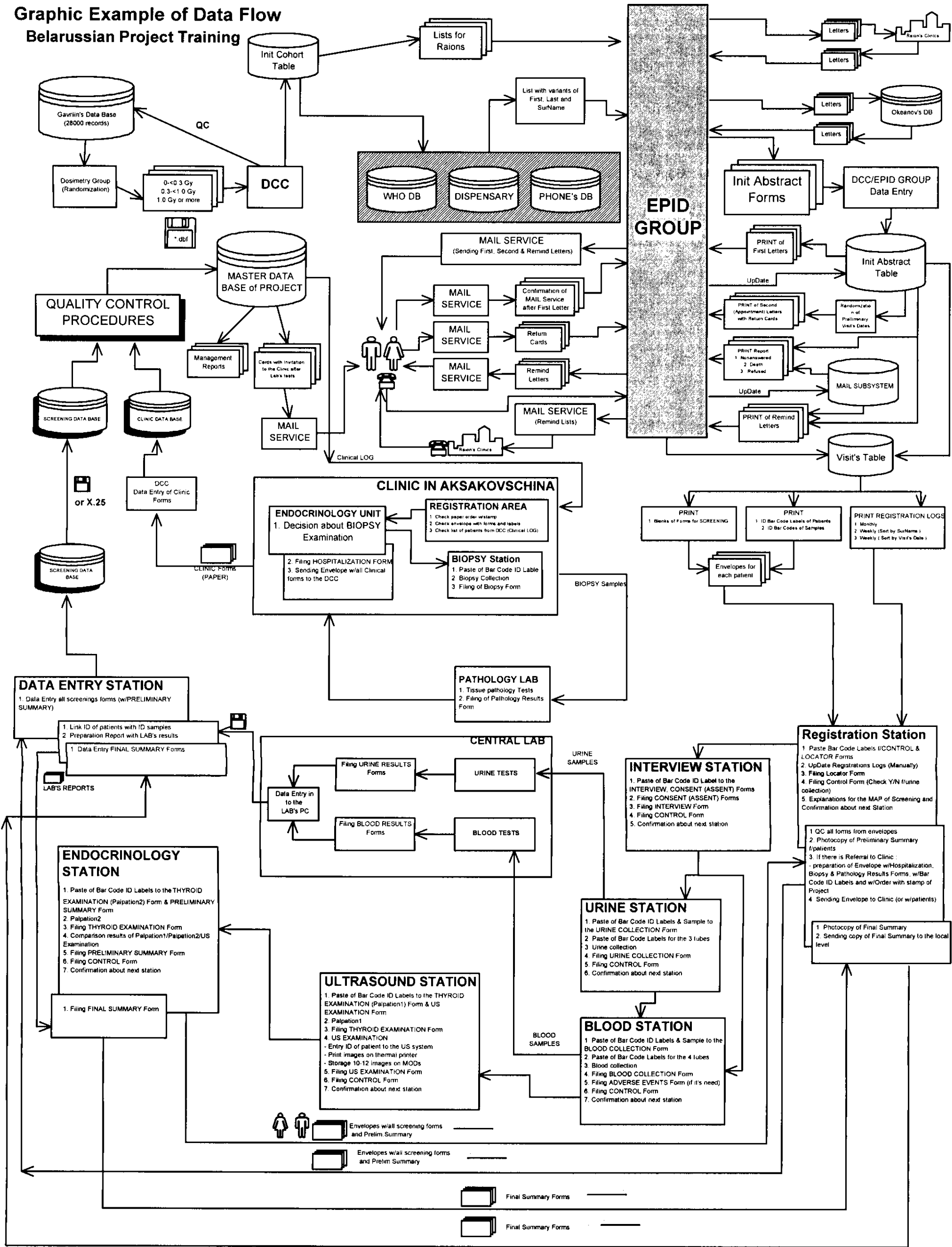
**UkrAm Project Director  
Institute Director**

**AMERICAN COMPONENT OF BI-NATIONAL ADVISORY  
GROUP ALSO ADVISORY TO NCI PROJECT DIRECTOR**

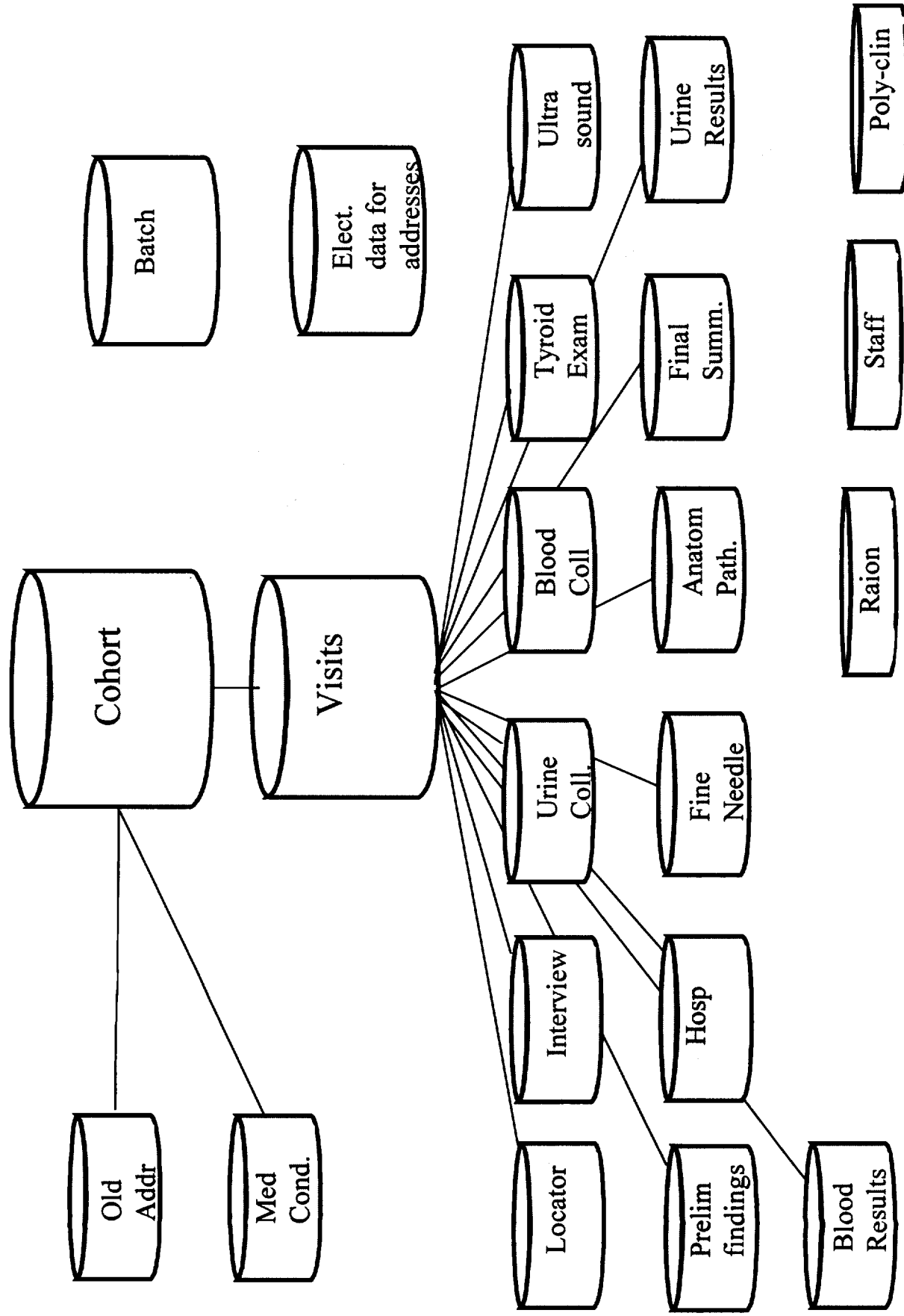
## **ROLE OF BINATIONAL ADVISORY GROUP:**

- **Respond to requests for advice from Project Directors**
- **Recommend changes/modifications to research protocols**
- **Review budgets presented**
- **Review progress of the work**
- **Advise on publication policy**
- **Initiate own agenda topics and investigations**
- **Determine its own operating rules and membership rotation order**
- **Advise on continuation or possible termination of projects**
- **Has the option of convening in a closed executive session**

Graphic Example of Data Flow  
Belarussian Project Training



# BELAM Database Structure



**STUDY OF THYROID CANCER  
AND OTHER THYROID DISEASE IN UKRAINE  
FOLLOWING THE CHERNOBYL ACCIDENT**

**MANUAL OF OPERATIONS**

December, 1997

**INSTITUTE OF ENDOCRINOLOGY AND METABOLISM  
ACADEMY OF MEDICAL SCIENCES OF UKRAINE**

**RESEARCH CENTER OF RADIATION MEDICINE  
ACADEMY OF MEDICAL SCIENCES OF UKRAINE**

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## 1. INTRODUCTION TO THE STUDY

This chapter presents an introduction to the Study of Thyroid Cancer and Other Thyroid Disease in Ukraine Following the Chernobyl Accident. It includes an overview of the study design, background information, objectives and a discussion of the purpose and organization of this document, the Manual of Operations.

### 1.1 OVERVIEW OF THE STUDY

The nuclear power plant accident at Chernobyl released large quantities of Iodine-131 and other radioisotopes of iodine into the atmosphere, contaminating thousands of square kilometers and exposing millions of people. For this study, a well-defined subset of Ukrainian children aged 0-18 years or in utero (born after 04.26.86 and before 01.31.87) at the time of the accident will be identified and will be examined by well-trained specialists for thyroid disease annually for up to 30 years. The study is a collaborative effort of researchers in Ukraine and the United States.

The cohort will include approximately 50,000 persons who were children in 1986, all or most of whom had their thyroids measured for radioactivity during the weeks immediately following the accident (or whose mothers had measurements taken while the child was in utero). Under a rigid research protocol these subjects will receive diagnostic thyroid examinations, including palpation, ultrasound scanning, thyroid hormone and other laboratory tests, and fine-needle aspiration biopsy. Interview information regarding residential, health, diet and lifestyle history will also be collected. All subjects will be followed for thyroid cancer morbidity and mortality. Thyroid cancers will be confirmed by expert pathology examination of tissue.

In addition to the analysis of thyroid radiation measurements in May-June, 1986, efforts will be made to reconstruct each subject's exposure and to estimate the radiation dose to the thyroid. This will involve the reconstruction of deposition patterns and environmental pathways of the radioiodines, and the location, dietary characteristics, and lifestyle of each person throughout the exposure period. The procedures used to estimate dose to the thyroid are not part of this manual.

An overview of data collection activities for the study is shown in the flowchart in Figure 1.

### 1.2 BACKGROUND

There is ample evidence that external radiation is associated with thyroid cancer, and a number of reliable epidemiological studies show that the risk is appreciable and that the thyroid gland is one of the more sensitive human tissues (Shor 1992). Moreover, the magnitude of risk is related to age at irradiation, and is higher for children than for adults. Thus, for subjects irradiated under the age of 20 years, the (weighted mean) absolute risk is 2.6 excess cancers per 10,000 persons  $\text{yr}^{-1} \text{Gy}^{-1}$ . Available data are consistent with a linear dose response curve over much of the exposure range, although cell killing may flatten such curves at very high doses. It is noteworthy that risk of thyroid cancer has been associated with external radiation doses as low as 0.09 Gy (Ron et al., 1989).

The thyroid gland is potentially at risk in the presence of radioactive fallout. This is due in part to its ability both to concentrate iodide by a factor of about 10,000 above ambient iodide concentrations and to incorporate iodide into thyroglobulin, which has a slow turnover rate. As a result, the effective half life of iodine isotopes (except  $^{129}\text{I}$ ) is nearly as long as the physical half life.

There has been considerable interest in the nodule and cancer risk associated with internal irradiation from iodine isotopes (chiefly  $^{131}\text{I}$ , half life of 8.05 days). The most reliable data, with good statistical power, derive from long-term follow-up studies of patients receiving diagnostic or therapeutic doses of  $^{131}\text{I}$ . No significant excess thyroid cancer was observed in these studies of mainly adult patients. It is uncertain to what extent these results are influenced by the possibility of preexisting thyroid disease for which these procedures were carried out. In two large studies of subjects treated for hyperthyroidism with mean doses of 88-113 Gy, similarly, there was no increase in risk for thyroid cancer. Estimation of the risk of thyroid disease, including cancer, resulting from exposure to  $^{131}\text{I}$  contained in fallout from atmospheric nuclear weapons tests is much more complicated, primarily because the radiation dose to the thyroid must be reconstructed.

There have been two studies of health effects resulting from exposure to fallout from atmospheric nuclear weapons tests. Both of these studies have used dose reconstruction techniques such as those referred to above. In a study of children living (at the time of the tests) in Utah downwind from the Nevada Test Site, the small excess of thyroid cancers was not statistically significant (Kerber et al., 1993). The absolute risk of persons in the Marshall Islands exposed to fallout was 1.1 and 1.3 per 10,000 subjects  $\text{yr}^{-1} \text{Gy}^{-1}$  for children irradiated under 18 years of age or for adults, respectively. Six excess cancers were observed in children during the first 35 years after the fallout occurred (Robbins and Adams, 1989).

Attempts have been made to explain the remarkable difference in the rates of thyroid-cancer induction caused by external and internal irradiation. Dose rate is considered to play a major role: most data

on external irradiation were obtained from acute doses. In studies where divided doses were given the risk appeared to be decidedly smaller (Shore 1992). It has been suggested that the intermediate risk of thyroid cancer for the Marshall Island population reflects the fact that about 80% of the dose is derived from the short-lived isotopes ( $^{132}\text{I}$ ,  $^{133}\text{I}$  and  $^{135}\text{I}$ ; and <10% external) with about 15% from  $^{131}\text{I}$  (Lessard et al., 1985). By contrast the diagnostic and therapeutic use of  $^{131}\text{I}$  implies a rather low dose rate. Whether the apparently low Effectiveness Factor (EF) for  $^{131}\text{I}$  has other causes is not clear at present and animal studies are inconclusive.

In addition to thyroid nodule and thyroid cancer, external radiation of the head and neck can also result in a variety of other tumors (Schneider et al., 1985) including parathyroid adenomas and hyperparathyroidism (Cohen et al., 1985). Because of their proximity to the thyroid gland, the parathyroid glands may also be at risk from exposure to radioiodines, as have been shown in experimental animals (Wynford-Thomas V. et al., 1982) and possibly in children who had received therapeutic  $^{131}\text{I}$  for Graves Disease (Esselstyn et al., 1982.)

The accident at Unit 4 of the Chernobyl nuclear power plant, which occurred in April 1986, was the most severe in the nuclear industry. The accident caused the death of 31 power plant employees and firemen from acute radiation exposures and burns, and resulted in the contamination of vast territories of Ukraine, Belarus and Russia. Radioactive materials were released into the atmosphere during a period of ten days. The radionuclides that are responsible for most of the radiation doses received by members of the public are  $^{131}\text{I}$ ,  $^{134}\text{Cs}$ , and  $^{137}\text{Cs}$ . The  $^{131}\text{I}$  and some shorter-lived radioisotopes of iodine caused high thyroid exposures, especially among children, during the first few weeks following the accident. The longer-lived  $^{134}\text{Cs}$ , and, more importantly,  $^{137}\text{Cs}$ , deliver doses to the entire body and will be present in the environment for decades to come. An increase in thyroid cancer in children was reported by Kazakov et al., in 1992.

The Chernobyl power plant is located in Kiev oblast of Ukraine. A fraction of the radioactive material present in the radioactive cloud was deposited on the ground, essentially as a result of scavenging by precipitation. The contamination of the ground resulted, in turn, in the contamination of milk and other foodstuffs.

Since the Chernobyl accident in 1986 the staff of the Institute of Endocrinology and Metabolism, examined tens of thousands of children in heavily contaminated areas of Ukraine. The examinations have routinely included ultrasonography and extensive laboratory tests. Preliminary evidence is currently available which links the Chernobyl accident with a subsequent increase in thyroid cancer among children. By 1<sup>st</sup> of January 1997 923 patients with thyroid cancer who were aged 0-18 at the time of Chernobyl accident have been operated (604 of them were 0-14 years at the time of accident).

The present study builds on that experience within an epidemiologic framework calculated to create dose-specific information on the risk of thyroid disease following exposure to  $^{131}\text{I}$ . A cohort of approximately 50,000 exposed children will be identified and examined annually for thyroid abnormalities for a period of 20 to 30 years.

### 1.3 OBJECTIVES

This collaborative investigation possesses both scientific and public health objectives. The scientific objective of the study will be to provide new knowledge on the correlation of thyroid diseases with radiation dose. The aim of the study will be to carry out valid and credible assessments of the early and late morphologic and functional changes in the thyroid glands of persons exposed to radiation from radioactive materials released as a consequence of the Chernobyl nuclear power plant accident. The emphasis is on dose-and time-specific changes, including but not limited to the following specific topics:

- Risk estimates, as a function of dose, for morphologic changes (i.e., nodules and cancer) in relation both to sex and to age in 1986; comparison of the relative effectiveness of  $^{131}\text{I}$  with that of published x-ray and gamma irradiation in inducing thyroid nodules and cancer.
- Risk estimates, as a function of dose, for induction of hypothyroidism and autoimmune thyroiditis in relation both to sex and to age in 1986.

In the course of the study other possible risk factors will be examined including dietary iodine intake during and after 1986, and the ingestion of potassium iodide for thyroid protection shortly after the accident.

The intended study also possesses practical public health objectives and implications. Most importantly, the study will provide guidance for the mitigation of the effects of the Chernobyl accident on thyroid disease in those exposed as children. It may also provide the basis for a radiation protection policy with respect to thyroid disease, not only in Ukraine but wherever nuclear power plants exist. The administrative implementation of the study will enhance the training and experience of younger specialists, not only in endocrinology and ultrasonography, but also in modern research methods appropriate for clinical follow-up studies, clinical trials of therapy, and case-control studies.

Finally, the establishment of a large fixed cohort and associated database on children and their parents will make available an asset that can be used for many other studies of the effects of the Chernobyl accident.

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## 2. PURPOSE AND ORGANIZATION OF THE MANUAL OF OPERATIONS

The purpose of this manual is to provide documentation of all study procedures except dosimetry. It is expected that this manual will be used as a resource by all members of the study team. The manual will be updated to reflect changes in procedures over the course of the study, all changes to be dated and certified by both UA and US representatives. The English and Russian versions must be in agreement. The Director is responsible for ensuring that updates are distributed to all holders of the manual.

The manual has been structured so that sections dealing with procedures for a particular task can be readily identified and can be provided to the individual involved in that particular task.

Descriptions of study procedures are given in Chapters 3-8 of the manual. Chapter 9 presents an overview of data management activities. The appendices which follow Chapter 9 contain the data collection forms and instructions for their use and samples of other study materials such as contact letters, logs and management forms and reports.

## 3. DEFINITION OF STUDY COHORT

In order for subjects to be included in the study cohort they must fulfill certain eligibility criteria. These criteria are detailed below.

### 3.1.1 ELIGIBILITY CRITERIA

The eligibility criteria are as follows:

1. The subject must have had direct radiation measurement of the thyroid in 1986 according to the file maintained in the Research Center of Radiation Medicine. For the in utero exposed, it is the measurement of the mother's thyroid that determines eligibility.
2. The subject's date of birth must fall in the interval 26 April, 1968, through 31 January, 1987.
3. The subject must be a resident of Ukraine at the start of the study.

### 3.1.2 POSSIBLE REASONS FOR EXCLUSION

There are no medical exclusion criteria for the study, including thyroid diagnoses already made.

The dosimetry group will use its judgment in omitting from the sample selection children with radiation measurements that are known to be useless.

It should be noted that following initial sample selection, loss to follow-up will occur for a variety of reasons including:

- subjects who cannot be identified or located
- subjects who emigrate from Ukraine
- subjects who are too ill to participate
- subjects with physical or mental impairment which precludes participation
- subjects who moved from the catchment area

Subjects initially selected will always remain part of the cohort. Reason for subject non-participation will be documented in the study management system (see Chapter 9).

### 3.2 SELECTION OF THE COHORT

#### 3.2.1 INITIAL STEPS

The dosimetry group of the Research Center of Radiation Medicine will provide a copy of the measurement file for children 0-18 in 1986 (see the research protocol, Section 3.2, Table 3.2.1) from which the epidemiology group and the data coordinating center will make the initial selection on the basis of the estimated dose, residence at exposure, and apparent adequacy of information. All decisions made during sample selection will be carefully and completely documented.

Although the protocol call for an 'intensive sample' of 50,000, the expectation is that a manageable cohort will be smaller, perhaps in the range of 30,000-40,000. Accordingly, an initial selection (Selection 1) of about 20,000 will be made, as follows:

1 or more Gy	all 9,800 available
0.3 - .9 Gy	5,000 from the 18,500 available
<0.3 Gy	5,000 from the 46,100 available

Selection from the two lower dose groups is to be made at random from the file. Subsequent selections will be made when the desired cohort size becomes fixed.

Additional details of the sample selection are provided in Appendix K.

#### 3.2.2 THE IN UTERO GROUP

Since the measurements file will contain no direct measurements on the in utero exposed, their selection will depend on the availability of maternal measurements. Dosimetry Registry of Research Center of Radiation Medicine transfer information they have pregnant women to epidemiology group and DCC. The epidemiology group will examine birth records and/or hospital records from the obstetric hospitals which serve the catchment area for births in the interval 26 April, 1986 and 31 January, 1987, abstract names and addresses of parents, and provide the list to the dosimetry group for record linkage to identify in utero exposed with maternal measurements.

### 3.3 ASSIGNMENT OF STUDY IDENTIFICATION (ID). NUMBERS AND SPECIMEN IDENTIFICATION NUMBERS

Study identification (ID) numbers will be assigned to each study subject after the initial selection has been made from the dosimetry file (without regard for any subsequent events that may result in non-participation). The file of selected study subjects will be sorted in random order before subject ID assignment to avoid having the subject's ID number indicate his probable dose range. After the random sort, the ID numbers will be assigned sequentially.

The ID number will consist of 8 digits: 6 for the individual's unique number, and 2 for the check number. The check number will be assigned as the sum of the 6 digits in the unique number.

The ID number will be used to identify the individual subject on all data associated with that subject. No ID number, once assigned, can be reassigned to another participant, changed or deleted. If the subject becomes ineligible after the ID has been assigned, the ID will **not** be reassigned. This policy ensures that data associated with a subject will not be lost or inadvertently attributed to another subject.

In addition to the subject ID number, separate, unique specimen ID numbers will be used. These numbers will be assigned to the blood samples collected from the study subjects each year, and the urine samples collected on a subsample of the study population in the baseline year. The link between the subject and his specimens will be made through these specimen ID numbers which will be placed on the blood and urine collection forms (along with the subject ID) and keyed into the study computer system. Blocks of specimen ID numbers will be assigned by the data coordinating center for each calendar year. The structure of the specimen ID number is: 1st 2 digits=calendar year, 3rd-8th digit=sequential number. In the end of ID number will be added a letter, appropriate to the type of the sample ( 'K' for the blood samples, 'M' for the urine samples, for example: 97000001K).

ID labels will be generated for both subject ID and specimen ID numbers which can be applied to the forms and specimen collection and storage containers. These will be provided by the data coordinating center. Two types of subject ID labels may be generated. The first type may contain the subject ID number

only, and the second may contain the subject's ID along with other identifiers such as name and date of birth.

Specimen ID labels will contain numeric information only, and may be used to identify the facility at which the screening took place.

### 3.4 ABSTRACTING RECORDS BEFORE INITIAL CONTACT

Preliminary demographic and identifying information will be collected on each subject selected for the cohort, mainly to provide information which will be useful in making contact with study subjects. It is expected that computer sources will mainly be consulted to obtain this information. The specific items of information to be collected are:

- Full names of subject, parents, as well as other family members or providers
- Date of birth of subject
- Address on 26 April, 1986
- Date of and location where the thyroid was measured
- Addresses subsequent to 26 April 1986, with dates
- The documentation of any information pertaining to thyroid disease that may be seen in any of the record sources, with identification of the condition and of the source, and of any applicable date of the condition, such as date of diagnosis.

This information will be recorded on the **Initial Abstract Form** and entered directly into a computer file or loaded onto the study computer from other files. Organizational responsibility for this work will be assumed by the Epidemiology Group and the data coordinating center. The Initial Abstract Form and instructions for its use are listed in Appendix A-3-1.

Sources from which the above information will be obtained may include:

- Database of clinic in Institute of Endocrinology & Metabolism
- Files of Ukrainian Center of Informational Technologies and National Registry Ministry of Public Health of Ukraine (Chornobyl Registry)
- Paper files of rayon polyclinics
- Local rural and urban authorities (selsky sovet, etc)
- Special departments of different ministries (military, internal affairs, public education)

It is not expected that **all** sources will be consulted for all subjects. Initially, information will be sought by linking any available computer files, most notably the national registry of Chernobyl victims and other files of the Research Center of Radiation Medicine. The material taken from these various files will be edited for consistency.

### 3.5 OBTAINING CURRENT ADDRESSES

Before allocations can be made to the individual examining teams by the data coordinating center, at least some addresses will have to be obtained. The effort to obtain addresses will be a continuing and intensive effort by the epidemiology group and the data coordinating center for the first three years of the study. Subsequent steps will include:

- record linkage with all available computer files;
- available paper files of the Institute of Endocrinology
- files of appropriate ministries;
- urban and rural authorities of localities where subjects lived on 26 April 1986; and mailings to verify addresses.

### 3.6 ALLOCATION OF SUBSAMPLES TO EXAMINING UNITS

The examinations will be performed principally in one fixed center, and in the field by three mobile teams. When a sufficient number of subjects has been located, a tentative map will be prepared to define the geographic boundaries of the areas of responsibility for the examining units. Ideally these boundaries should be mutually exclusive. In the aggregate they constitute the catchment area.

It is to be expected that, over time, as the study matures, there will be changes in the precise boundaries of the areas served by the examining units, as well as in the assignment of subjects to particular examining units. There will be subjects who initially reside outside the geographic boundaries of catchment area. However, in subsequent years, as boundaries change, or members of the cohort move into the catchment area, they should be included into the screening process. It is important, therefore, that all members of cohort be tracked and contact be maintained.

### 3.7 SUPPLEMENTATION OF THE INITIAL LISTING

If, during the first three years, sample losses from refusal, emigration, and failure to locate, appear to require it, consideration will be given to a re-selection of potential subjects from the file of measurements and/or selection of subjects with only passport doses. The re-selection will employ the same principles as

governed the initial selection and will be reviewed by the study advisory group to ensure that sound scientific principles are applied.

## 4. CONTACT PROCEDURES

### 4.1 PUBLICITY

Before contact is made with individual families, the Ministry will mount a publicity campaign in the mass media and through medical channels. Local and central newspapers, radio, and television will all be employed to explain the purpose and the content of the study. The publicity will stress the value of the study to the health maintenance of the individual. The schedule for publicity will need to be carefully timed given that there will be somewhat of a gradual start to the study. Material may need to be repeated throughout the first year of the study and beyond as deemed appropriate.

### 4.2 INITIAL CONTACT WITH STUDY SUBJECTS

The data coordinating center and epidemiology group will take the leading role in initial contact with study subjects and their parents. It will be important for a parent to accompany the study subject to the first visit in order to provide the most accurate information needed for dose reconstruction. The family (or adult subject) will first receive a letter from the deputy Minister of Health describing the study and its benefits to the individual, specifying the place of examination and an appointment time and date or a range of dates with information on how to arrange and confirm appointments by postcard and telephone. This letter will be sent out by the data coordinating center. With the letter will be a pre-printed, stamped card to be mailed back to the epidemiology group. It will provide for confirmation of the offered appointment, a request for an alternative or deferred appointment, and a telephone number (if available) where the subject and his parents may be reached. As this cards came to the epidemiology group, sorted out, Initial Abstract Form filled out, Data coordination center will make Registration Log and will forward it to the fixed or Mobil team. If the subject and accompanying parent do not appear for the scheduled appointment, the fixed or mobile team will inform the data coordinating center, they will inform epidemiology group, which will follow-up this contact and conduct any further scheduling activities. Copies of the letter and appointment confirmation card are in Appendix C-4-1.

#### 4.2.1 HANDLING NON-RESPONSE

There are three major categories of non-response. The first is inability to locate the subject. This may result from having an incorrect address in the study records, from having an old address (the subject has moved) or having no address at all. The second major category is inability to contact the subject. Attempts to reach the subject, either by mail or by phone, may be unsuccessful. The third category is refusal. Subjects (or their parents) may be reluctant to participate due to a misunderstanding of study objectives, a negative attitude toward medical examinations or other reasons.

The data coordinating center will be responsible for informing the epidemiology group of non-response subjects who require follow-up. The epidemiology group will be responsible for coordinating appropriate follow-up activities and reporting on them to the data coordinating center. Some initial steps such as sending a second letter, attempting a telephone contact or sending a registered letter will be carried out by the data coordinating center. Support from local medical authorities at the raion level will be sought for locating, contacting and convincing reluctant subjects to participate. This support will be officially requested from the Minister of Health.

For subjects who cannot be located or contacted, lists will be sent to the local medical authorities at the raion level to request their assistance in locating the subjects. For refusals, the epidemiology group will provide the local medical authorities with the reasons for refusal and request that they contact the subjects in the attempt to involve them in the study. It is felt that this approach may be effective since local medical personnel are more familiar with specific issues in their region and are psychologically closer to the inhabitants of the individual raion. It is also possible, due to closer proximity, that local medical personnel may be able to discuss the study with the subject, **in-person**. Such direct contact may result in better communication and therefore more success in convincing reluctant subjects to participate.

Other possible tracing sources include databases which cover large segments of the population. The epidemiology group and the data coordinating center will be on the lookout for appropriate databases suitable for record linkage by computer. The Chernobyl Registry is an example.

### 4.3 OBTAINING INFORMED CONSENT

Informed consent (or assent) will be obtained through a written informed consent statement (Appendix B-5-1) which will be read to or by the parents of children or to adult subjects. The subject or parent will then be given an opportunity to ask any questions. No signatures will be required of the parent, child or adult subject but the staff person who administers the form will note, and initial, the fact of acceptance or refusal. Informed consent will be obtained during the initial clinic visit as described in Section 5.1.

#### 4.4 SCHEDULING SUBJECTS FOR EXAMINATION

The study eventually plans to provide examinations for perhaps 30,000 - 40,000 children and adult subjects (final number to be determined), and for examinations to be repeated at yearly intervals. During the first full twelve months of the study, after pilot work has been performed, it is expected that perhaps subjects will be examined, in the second year, and about in the third year.

##### 4.4.1 INDIVIDUAL APPOINTMENTS

The fixed or mobile team and the data coordinating center will agree on an anticipated flow of subjects for examination over a fixed period of time. The data coordinating center will make a selection of subjects, send the initial letter from the deputy Minister of Health with the information about appointment. The epidemiology group center will then be responsible for appointment confirmation and Data coordination center will take care about re-scheduling. Names and other identifying information, and dates of confirmed appointments, will be provided by the data coordinating center to the fixed team over the computer network.

Appointment making for a mobile unit will be handled by the data coordinating center in the same manner as making appointments for fixed team visits. The data coordinating center and epidemiology group will similarly be responsible for appointment confirmation and re-scheduling.

The data coordinating center may also carry out some initial follow-up activities with non-responders such as sending a second letter, or making a phone contact. Those who do not respond to these efforts will be referred to the epidemiology group for further follow-up (see Section 4.2.1).

For appointments made more than a month in advance, subjects will be sent a reminder notice from the data coordinating center a few days before the scheduled appointment. Subjects may also be called the day before to confirm the appointment and answer any questions, if it is known that the subject can be reached by telephone.

##### 4.4.2 CONTROLLING THE FLOW OF SUBJECTS TO EXAMINING CENTERS

The data coordinating center will maintain a record of appointments made for each subject, dates of examinations, and will re-schedule subjects for examination yearly on the basis of the capacity of the fixed or mobile team. Every effort will be made to schedule annual examinations within plus or minus one month of the date of the subject's baseline examination. This time period is referred to as the visit "window."

#### 4.5 MAINTAINING CONTACT WITH MEMBERS OF THE STUDY COHORT

At the initial screening visit, the subject will be asked to provide information which will help locate him in the future. This information will be recorded onto the **Locator Form**. The form and its specifications appear in Appendix B-5-2. Items of information on this form include complete name of subject and parents, present address and telephone number, complete date of birth, indication of any plans to move, the names and addresses of two close relatives or friends who do not live in the subject's household but would know his whereabouts and the name of the subject's home polyclinic. The Locator Form will be reviewed with the subject and updated as necessary at each annual clinic visit.

The data coordinating center will be responsible for informing epidemiology group of non response subjects who require follow up tracking efforts, epidemiology group will be responsible for follow-up activities and reporting their results to the DCC. Some initial steps, such as sending second letter, a second telephone contact, or sending a registered letter may be carried out by the coordinating center or by the supporting facility in the field. Support from local medical authorities at the highest level will be sought for locating, contacting and convincing reluctant subjects to participate. This support will be officially requested from the ministry of Health.

Other possible tracing sources include data bases that cover large segments of the population. The epidemiology group and the DCC will look out for appropriate data bases for record linkage by the computer. The Chernobyl Registry is an example, especially since it is continuously updated.

#### 4.6 DOCUMENTING PARTICIPANT STATUS

The status of each study subject will be tracked through the study computer system. Information will be entered to indicate whether the subject is an active participant, has refused, is lost to follow-up, or has moved outside Ukraine. The participant's status in terms of completion of data collection activities will also be maintained in the system. Documents describing reasons for refusal or steps taken to trace a lost subject will also be used and will be filed with the data coordinating center (see Chapter 9). The data coordinating center will provide the examining groups, as well as the epidemiology group with monthly or quarterly reports on patient participation.

#### 4.7 HANDLING OF INDIVIDUALS WHO ARE NOT COHORT MEMBERS BUT WISH TO BE EXAMINED UNDER THE RESEARCH PROTOCOL

If a person approaches a fixed or mobile team for examination and time is available, he may be offered palpation and ultrasound examination of the thyroid. However, blood would not be drawn and a written result would not be made. In the case of an abnormal finding, he would be referred to a polyclinic or hospital, as appropriate.

## 5. EXAMINATION PROCEDURES

The examinations will be performed in fixed center and by mobile teams. There will be one fixed team in the Institute of the Endocrinology and Metabolism and 3 mobile teams. The subject will ordinarily arrive with his appointment card in hand. He is to be welcomed and thanked for coming. The subject will be directed through the various examination stations where he will be interviewed, provide a blood sample and a urine sample (baseline year only) and have the thyroid ultrasound and thyroid palpation examinations. At the end of the examination process the subject will receive the Preliminary Summary of Medical Findings and Recommendations (next visit in a year, check-up in six months, referral to hospital, etc). A copy of this summary will remain in the subject's chart.

### 5.1 REGISTRATION AND INFORMED CONSENT

When the subject enters the examining area, he will be greeted by the registration nurse, who will carry out registration activities. The arrival of the subject will be documented in the Registration Log (Appendix B-5-1). The Registration Log will have been prepared in advance (printed with the identification numbers, names and dates of birth of scheduled subjects) by the data coordinating center. Mobile team will receive Registration Log from DCC before their trip.

If this is the first visit, the subject's identifying characteristics (full name, full date of birth, present address and telephone number if available, and parental names) and name of home polyclinic will be obtained/verified. This information will be recorded on the **Locator Form** (see also Section 4.5). Other information recorded on the Locator Form includes an indication of any plans to move and the names and addresses of two close relatives or friends who do not live in the subject's household but would know his whereabouts. This form will be administered by the registrar. At each annual visit, the information on this form will be reviewed and updated, as necessary. The Locator Form and its specifications are in Appendix B-5-2. At the first visit, the informed consent statement will be read to or read by the subject or an accompanying parent.

If the subject is under 16 years of age, oral parental consent to the examination will be sought from an accompanying parent and the assent form will be read to the subject. If the subject is 16 or older, consent will be sought from the subject directly. Informed consent will be obtained once for the entire study and need not be obtained again during subsequent examinations. The informed consent statement is shown in Appendix B-5-1. (The consent may be administered by the interviewer at the interview station. It is important that it be administered before any data collection activities are initiated.)

The subject's envelope will contain all necessary labels for the study forms (except for specimen labels) and the study **Control Form**. At each examining station, the study personnel will remove a label from the subject's envelope, label and complete the study form, and return the form to the subjects envelope. Specimen labels for the Blood and Urine collection forms, as well as for specimen containers will be attached at the specimen collection and processing stations. The envelope will also contain the Control Form. The Control Form will reflect whether or not the subject is required to complete the urine collection procedure. Urine collection will only be required if the subject was pre-selected for urine collection (see Section 5.2.2). Information will also be recorded on this form by the examiner at each examination station to indicate whether the particular exam component was completed. The Control Form and instructions for its use appear in Appendix B-5-4. After receiving the envelope, the subject will be directed or taken to the first examining station where interviewing takes place.

### 5.2 SEQUENCE OF EXAMINING STATIONS AND PATIENT FLOW

The usual sequence, especially in a fixed examining center will be as follows:

- Interview
- Urine collection
- Blood collection
- Clinical examination and thyroid palpation
- Thyroid ultrasound

The sequence of urine and blood collection may be varied by mobile teams. However, the ultrasound/thyroid palpation order will always be maintained. The subject first will be seen by the ultrasonographer who will, however, perform thyroid palpation before the ultrasound examination (see Section 5.2.4). If the patients flow is big, subject might be seen first by the endocrinologist and then by the ultrasound specialist.

After the examination endocrinologist will fill out Preliminary Summary of Medical Findings and Recommendations.

#### 5.2.1 INTERVIEW

Interview forms and content differ for first vs subsequent visits. The interviewer will welcome the subject and the accompanying parent and explain the purpose of the interview and its content, relating it to health maintenance as much as possible. The interviewer will remove the labeled interview form from the package brought by the subject and proceed with the interview. The interviewer will enter the replies to the questions asked on the form and will print and sign his name on the completed form. Before releasing the subject the interviewer will scan the form for any gaps or inconsistencies that might be corrected before the subject leaves the station. At the conclusion of the interview the subject and the accompanying parent will be asked if there are any questions that the interviewer might answer. If medical questions are asked, they will be advised to take them up with the endocrinologist after the thyroid examinations.

The **Initial Interview Form** is shown in Appendix A-5-1. Specifications for administration of this questionnaire are also included in this Appendix. The **Annual Interview Form** used in subsequent years of the study is in Appendix A-5-2 along with instructions for its administration. General interviewing techniques are provided in Appendix D. These techniques provide the fundamental principles with which interviews should be administered in the epidemiologic research setting. All interviewers will receive training on general interviewing techniques and on the interview forms before they begin administering the questionnaires.

Depending on the age of the child, the questions asked and period of time to be remembered, one of the parents can be considered as the most appropriate person to be interviewed. It should be clarified before the interview.

The Control Form will be marked to show that the interview was completed. The subject will be thanked for his contribution and directed to the next examining station. This may be for urine collection or for blood drawing.

The completed interview form will be placed in the collection box at the interview station pending pick-up by the data entry specialist.

### 5.2.2 URINE COLLECTION AND POST-COLLECTION PROCEDURES AT THE EXAMINING LOCATION

The protocol for urine collection calls for collection of urine only in the baseline year and only on a sample of subjects representing specific raions with the objective of collecting 80-100 samples per raion.

Subjects selected for urine collection will be pre-designated by the data coordinating center. The examining center will receive a list of subjects selected for urine collection. The requirement to complete the urine collection procedures will be reflected on the subject's Control Form.

#### 5.2.2.1 RATIONALE

Estimation of the content of the iodine in urine will help to characterize the existing iodine deficiency, there spreading and grade in the examining regions of Ukraine.

#### 5.2.2.2 EQUIPMENT AND SUPPLIES

Supplies needed for the urine collection include:

- Urine collection containers with lids
- Urine Collection and Processing Form
- Specimen ID labels

Supplies needed for processing urine samples at the examining center include:

- Urine transport tube with cap, 2 per person  
(CMS Catalog, p. I-338)
- (NOTE: A falcon tube with conical bottom may be preferable because the tubes can be placed easily into a Styrofoam rack for storage and shipment.)

- Rubber gloves
- Disposable pipets
- Urine Collection and Processing Form
- Specimen ID labels

Supplies needed for local storage and shipment of urine samples include:

- Storage boxes (or racks)
- Plastic bags
- Shipping boxes
- Transmittal Form

#### 5.2.2.3 TRAINING AND CERTIFICATION OF PERSONNEL

Collection and processing of the urine will be handled by the nurse-assistant. Training on processing, storage and shipping procedures will be conducted by staff of the Central Laboratory. No certification of personnel will be required.

#### 5.2.2.4 INSTRUCTIONS FOR URINE COLLECTION

Urine collection will be administered by the nurse assistant. He will first determine the eligibility of the subject for the collection. This will involve questioning the subject about current thyroid hormone medication

usage. Urine samples will not be collected from persons taking thyroid hormones. If eligible, he will label the Urine Collection and Processing Form with one of the attached specimen ID labels and proceed to ask the subject about polyvitamin and other medication usage and record this information on the form (see Section 5.2.2.7).

The nurse-assistant will label the collection container with the specimen ID and instruct the subject to empty his bladder into the container. After producing the sample, the subject should replace the lid on the container and return it immediately to the nurse assistant. The nurse assistant will record the date and time of collection onto the Urine Collection and Processing Form and the fact of collection on the Control Form before sending the subject to the next station. It is very important that only provided containers be used - others might have contamination, i.e., a sample collected by the subject at home in his/her own container should not be used. Any sample with known iodine contamination should be marked and kept separate from uncontaminated samples.

#### **5.2.2.5 INSTRUCTIONS FOR URINE PROCESSING**

The urine sample will be accompanied to the urine processing station by a Urine Collection and Processing Form and additional specimen ID labels. (it is noted that the processing station may be in the same workspace as where collection was handled.) Processing of the sample should be done as soon as possible after collection. Urine samples collected by mobile unites should be refrigerated and tested preferable within a week, otherwise, a drop of sodium hydroxide will be added as a preservative.

Processing steps include preparation of two aliquots of 5 ml each. The two 5 ml transport tubes should be labeled with specimen ID labels and 5 ml of urine transferred by pipet into each tube. The remainder of the urine sample will be discarded. The time of transfer will be recorded on the Urine Collection and Processing Form.

#### **5.2.2.6 INSTRUCTIONS FOR STORAGE AND SHIPMENT OF URINE SAMPLES**

The urine aliquots will be placed into a storage box and stored under refrigeration (4<sup>0</sup> C.) until shipment to the Central Laboratory. Alternatively, the samples may be stored in racks. Shipments to the Central Laboratory will be made on a weekly basis. For shipment, the samples will be placed into a large shipping box, appropriately labeled. If stored in racks, each filled rack should be placed into a plastic bag first. A transmittal form will accompany each shipment. The transmittal will list the date and contents of the shipment i.e., a listing of all specimen ID's included in the shipment. A copy of the transmittal will be kept at the local facility and another copy will be sent to the data coordinating center.

#### **5.2.2.7 DATA COLLECTION AND TRANSFER TO DATA CENTER**

Information regarding urine collection and processing will be documented on the **Urine Collection and Processing Form**. The form will be pre-labeled with the subject ID number and have a set of specimen labels attached to it. After determining that the subject is eligible for the urine collection (i.e., not taking thyroid hormone medication), the nurse assistant will affix a specimen ID label onto the form and will record the polyvitamin, and medication information, the date and time of collection and any problems with the sample. The nurse assistant will then document the preparation of the two aliquots of 5 ml on the form. The form will be placed in the collection box for pickup by the data entry specialist. See Appendix A-5-3 for a copy of the Urine Collection and Processing Form and specifications for its completion.

If a urine sample is not collected on a subject who was pre-selected for urine collection, this fact will be recorded on the Control Form and the Urine Collection and Processing Form will not be completed. If the subject was not selected for urine collection, the urine collection box on the Control Form will be marked "not applicable."

The urine samples themselves will be shipped to the Central Laboratory accompanied by the Urine Collection and Processing Form and a transmittal form listing the date of shipment and ID numbers of all samples in the shipment (see Appendix B-5-5). Copies of the transmittals and data on diskettes will be sent to the data coordinating center. This will allow the data coordinating center to monitor the shipment of samples and track receipt of test results.

#### **5.2.2.8 QUALITY CONTROL**

Quality control for urine collection and processing will be implemented through the following steps:

- Direct observation of collection and processing procedures at the examining center by the Quality Control Officer.
- Ongoing evaluation of the number of subjects providing a urine sample. If the number is low, the reasons and possible solutions will be explored.
- Checking each lot number of transport tubes for possible iodine contamination. This will be done by the Central Laboratory who will control the supply of these tubes to the examining centers.
- Documenting the collection and reviewing any problems noted on the Urine Collection and Processing Form.
- Reviewing results from the laboratory testing to ensure that collection, processing, field storage and transport procedures are providing adequate samples for the test procedures.

- Checking the interval from collection to receipt at the Central Laboratory.

### 5.2.3 BLOOD COLLECTION AND POST-COLLECTION PROCEDURES AT THE EXAMINING CENTER

The same procedure as described for urine collection (see Section 5.2.2) will be followed for the blood draw. The phlebotomist will put the subject's ID label on the blood collection form, and along side it will be placed the unique specimen ID label. The remaining foil-back blood specimen labels will be placed on the aliquotted tubes. Ten ml. of blood will be collected aseptically into one 10 ml. serum separator vacutainer tube. The samples will be spun down to separate serum. The serum will be aliquotted into labeled cryovials, frozen to -20° C., and shipped periodically to the Central Laboratory for evaluation of TSH, anti-TPO and serum calcium. Blood samples collected in mobile units will be transmitted frozen to the Central Laboratory.

#### 5.2.3.1 RATIONALE

Assays to be performed on the blood samples will be used in the diagnosis of thyroid abnormalities (e.g., thyroid function abnormalities, autoimmune thyroiditis), parathyroid abnormalities and for the follow-up of thyroid pathology.

#### 5.2.3.2 EQUIPMENT AND SUPPLIES

The materials and supplies needed for the blood collection are as follows:

- 10 ml serum separator tubes; 1 per person
- Vacutainer needle holder, standard size
- Tourniquet, latex
- Alcohol wipes, individually wrapped
- Sterile gauze
- Band-aids (bandage strips)
- Test tube rack
- Biohazard bags
- Disposable gloves, latex, small, medium, large
- Blood Collection and Processing Form
- Specimen ID labels

It should be noted that vacutainer tubes should be at room temperature at the time they are used. They must be protected from extremes of temperature and stored at a constant temperature in a cool place. The vacutainers are also dated. Each box of tubes has an expiration date printed on it. Expired tubes should not be used.

Supplies needed for processing the blood samples include:

- 10 ml vial 1 per subject per draw
- 1.0 ml Cryovial closure color-coders, 3 per person per draw
- blue color - for immunoferment assay, 2 per person per draw
- green color - for Ca, 1 per person per draw
- Transport tubes, 2 per subject per draw
- Disposable Pasteur-type transfer pipettes (0.1-1.00 cm)
- Cryovial holder
- Blood Collection and Processing Form
- Specimen ID labels

The supplies needed for storage and shipment of processed samples are as follows:

- storage boxes
- map cards
- box labels
- transport coolers
- Blood Collection and Processing Form
- Transmittal Form

#### 5.2.3.3 TRAINING AND CERTIFICATION OF PERSONNEL

Blood collection will be performed by experienced and trained phlebotomists. Training in study-specific phlebotomy procedures (i.e., using vacutainers) will be carried out in a short 2-3 day course for all phlebotomists. No special certification will be required. The quality of the blood collection carried out by the phlebotomists will be evaluated through the success of their draws and the testing of the collected samples (see Section 5.2.3.9 below).

A laboratory technician will carry out the processing of the blood samples. Training and certification will be conducted by the Central Laboratory. Detailed written instructions on processing procedures will be prepared by the Central Laboratory. The laboratory technician will be required to familiarize himself with these procedures and will then perform them under the direct observation of Central Laboratory senior

personnel. After certification has been carried out, the names, dates and certification status of all laboratory technicians will be documented. This documentation will be kept on file at the data coordinating center. The data coordinating center will track the status of certification and advise the Central Laboratory when recertification is required. Recertification will be required on an annual basis.

#### 5.2.3.4 INSTRUCTIONS FOR THE BLOOD COLLECTION

##### *PREPARING FOR THE DRAW*

Before the blood sample is drawn, the subject should be questioned about bleeding disorders; extra precautions may be required in this situation. The subject should rest in a seated or reclining position for at least 5 minutes before the draw and remain in this position during the venipuncture. Having the subject sit or recline helps guard against any injury that might result if the subject faints.

It is extremely important that the anticipated puncture site and all necessary equipment, including needles and tubes be kept absolutely sterile and free from contamination. Extreme caution must be exercised throughout the collection of blood so that the data are valid and subjects and study workers are protected. Biosafety guidelines are provided in Appendix E.

Additional preparation steps for the phlebotomist include:

- Place the venipuncture equipment where it is readily available but not in danger of being upset. Keep extra equipment within easy reach.
- Thoroughly wash your hands.
- Put on gloves.
- Prepare the blood collection tube, placing it in a test tube rack until you are ready to use it and labeling it with the appropriate specimen ID label. Labels will be attached to the subject's Blood Collection and Processing Form.

##### *VENIPUNCTURE TECHNIQUE*

- Instruct the subject to extend the arm palm up and straight at the elbow.
- Position the arm on your work table so that the veins are readily accessible and you are able to work in a comfortable position. Be sure that the arm is in a downward position with the elbow lower than the heart to prevent backflow.
- Inspect the arm to use for venipuncture. The veins of choice are those located in the antecubital area. Do not draw blood from an arm which has a rash or open sore or is swollen or edematous.
- Apply the appropriate latex strip tourniquet several inches above the subject's elbow.
- Select a vein that is palpable and well-fixed to surrounding tissue. Palpate even when the vein can be seen. If the veins do not distend rather quickly, the following techniques may be used.
- Have the subject open and close the hand several times.
- Massage the arm from wrist to elbow; this forces blood into the veins.
- Tap the area sharply with the index and second finger two or three times; this causes the veins to dilate.
- The arm to be used for venipuncture may be hung at the subject's side without a tourniquet. This will allow the veins to fill with blood to their capacity.
- Examine the subject's other arm. Sometimes the veins in one are larger than in the other.
- If the tourniquet has been applied for more than one minute while you search for a vein, release the tourniquet for two to three minutes. Prolonged obstruction of blood flow by the tourniquet is unnecessary and uncomfortable for the subject, and may alter certain results.
- Check carefully for scar tissue or the presence of tendons near the vein.
- Cleanse the area with an alcohol wipe. Hold the alcohol wipe with two fingers on one side of it, so that only the other side of the wipe touches the area of the puncture site. Cleanse the area using a circular motion beginning with a narrow radius and moving outward so as not to cross over the area already cleansed. Repeat with a second alcohol wipe. Dry the cleansed area using a sterile 2x2 gauze pad. The area should be completely dry before the venipuncture is done in order to reduce the burning sensation caused by alcohol penetrating the skin.

##### *CONDUCTING THE VENIPUNCTURE*

- Open needle package and assemble vacutainer holder and the needle by screwing threaded end of needle onto the holder.
- Place the tube to be drawn into the holder, securing it slightly, but not penetrating the stopper.
- Ask subject to make a fist.
- Remove sheath from needle.
- The vein should be "fixed" or held taut during the puncture. Place the left thumb about one inch below the point of entry and pull skin gently in a downward motion. (This stretches the skin and "anchors" or "fixes" the vein.)
- Hold the needle in line with the vein, with the bevel up and at a 15° angle with the skin.

- Push the needle firmly and deliberately into the vein. As the needle enters the vein, you will notice a little "give."
- Quickly push the vacutainer tube into the holder, puncturing the stopper. Blood will be drawn into tube. If no blood enters the tube, and no bruise is forming, probe the vein until entry is indicated by blood flowing into the tube. If no blood enters the tube and a bruise is forming, release the tourniquet and remove the needle immediately. Do not keep probing for the vein as this can cause severe bruising. Place a gauze square over the puncture site and apply firm pressure to the puncture site for three minutes.
- HOLD THE TUBE IN A DOWNWARD POSITION, with the stopper uppermost.
- Release tourniquet as soon as good blood flow is achieved. (NOTE: It is important that the tourniquet be released as soon as possible. There is some evidence that leaving it on too long can affect the results of the calcium assay.)
- After the tube is filled to capacity, carefully pull it out of holder.
- Gently remove needle and holder assembly in a smooth quick motion, covering site with a sterile gauze pad.
- **Discard the needle without capping it in the needle disposal box.** When the box is full, place it into a biohazard bag along with any other contaminated waste paper.
- Immediately invert the tube 5 times, gently.
- Write the date and time of collection directly on the tube.
- Check the venipuncture site. If it is adequately clotted, apply tape over the gauze pad. Instruct the subject to remove it in no less than 45 minutes if the bleeding has stopped. Also, suggest that the subject sit quietly for a few minutes.
- If bleeding continues, keep direct pressure on the site for five minutes or more.
- Report any adverse reaction to venipuncture to a physician immediately.
- No more than 2 attempts may be made on one arm; in the event of failure with the arm of choice, the other arm may be used.
- For any vasovagal or syncopal episode, the subject will be instructed to put his head between his knees. An inhalant may be used. If the episode continues, a physician should be notified.
- Record the date and time of the blood draw and any problems onto the Blood Collection and Processing Form.
- Record the success of the blood collection onto the Control Form and direct the subject to the next station.

#### 5.2.3.5 PROCESSING PROCEDURES IMMEDIATELY AFTER THE BLOOD DRAW

The following steps will be carried out by the phlebotomist immediately after the blood draw is complete:

- The tubes will be allowed to stand (without being moved) at room temperature (18-20° C) for 30 to 45 minutes from the time of the draw. This is to allow complete clot retraction.
- The tubes will be transported to the processing station. (It is noted that the processing station may be in the same workspace as where collection was done.)

#### 5.2.3.6 PROCESSING THE BLOOD SAMPLE

The blood sample must be centrifuged, the serum separated from the clot and the serum samples aliquoted and frozen **on the day of collection**. The following steps will be carried out by the laboratory technician:

- Centrifuge the 10 ml tube in which the sample was collected for 15 minutes at room temperature at 1200 x g.
- Inspect the serum to determine if it is hemolyzed, icteric, turbid or lipemic. These problems should be documented on the Blood Collection and Processing Form.
- Prepare 3 storage vials by labeling them with the specimen ID labels and prepare colored caps (coders) in following order: 2 blue color - for immunoferment assay, 1- green color - for Ca. Specimen ID labels will be attached to the subject's Blood Collection and Processing Form.
- Using automatical pipets 0.8-1.0 ml of serum put into each of the vials covered with blue caps and 0.4-0.5 ml of serum in vial with green cap.
- Cap all tubes and vials. Put color labels as stated above.
- Record information about the results of processing the samples onto the Blood Collection and Processing Form.

#### 5.2.3.7 INSTRUCTIONS FOR STORAGE AND SHIPMENT OF BLOOD

All processed samples will be stored at -20° C in the refrigerator until they are shipped in the transport cooler to the Central Laboratory. Each storage box will be labeled with a box number and sample type to help identify it in the freezer.

Steps for storage and shipment of the blood samples are as follows:

- Each vial will be stored in a storage box. Vials should be placed into the next available slots within the appropriate storage box, keeping all samples of a particular subject in consecutive slots. The boxes will be filled in serpentine order.
- Once frozen, samples should never be thawed before testing at the Central Laboratory.
- Samples will be stored at -20° C until ready for shipment.
- Information about the storage location of the samples will be recorded onto the Blood Collection and Processing Form.
- Blood samples will be shipped in portable ice chests to the Central Laboratory on a weekly basis.
- A transmittal form will accompany each shipment. The transmittal will list the date and contents of the shipment (listing all ID's and number of vials per ID included in the shipment). A copy of the transmittal will be kept at the local facility and another copy will be sent to the data coordinating center.

#### **5.2.3.8 DATA COLLECTION AND TRANSFER TO DATA CENTER**

The blood collection and processing will be documented on the Blood Collection and Processing Form. This form will be pre-labeled with the subject ID and will have a set of specimen ID labels attached. The phlebotomist will label the form with the specimen ID number and will record information about the subject's status with regard to fasting, smoking, exposure to cold and exertion, polyvitamin and medication use, the date and time of the draw, and any problems with the draw. The phlebotomist may also maintain a blood collection log at the phlebotomy station in which the fact of each blood collection will be recorded.

The Blood Collection and Processing Form will accompany the sample to the processing station, where information will be recorded by the laboratory technician regarding processing and storage. The form will then go to the data entry specialist for entry into the study computer system. See Appendix A-5-4 for a copy of the Blood Collection and Processing Form and specifications for its completion.

If NO blood sample is collected, this fact will be recorded on the Control Form and no Blood Collection and Processing Form should be completed.

The blood samples themselves will be shipped to the Central Laboratory accompanied by a transmittal form listing the date of shipment and ID numbers of all samples in the shipment (see Appendix B-5-5). A copy of the transmittal will be sent to the data coordinating center. This will allow the data coordinating center to monitor the shipment of samples and track the receipt of test results. Completed Blood Collection and Processing Forms will also be sent to the Central Laboratory where they will be keyed (for a second time).

#### **5.2.3.9 QUALITY CONTROL FOR BLOOD COLLECTION AND PROCESSING**

Quality control for blood collection and processing will be implemented at the local fixed and mobile sites, at the data coordinating center and by the Quality Control Officer:

- Training and certification of the laboratory technicians.
- Ongoing evaluation of the number of unsuccessful draws and failure to obtain adequate samples. If the numbers are high, the reasons and possible solutions will be explored.
- Monitoring fainting or other episodes requiring consultation with a physician, as documented on the Blood Collection and Processing Form or Adverse Events Report.
- Reviewing processing problems reported on the Blood Collection and Processing Form. This will include comparison between the number of required cryovials and those actually frozen, problems with samples that are hemolyzed, icteric, turbid, etc.
- Local monitoring of the temperature of all freezer units. Units will be checked at the beginning and end of each working day, and appropriately logged.
- Monitoring of samples prepared and shipped outside the protocol window.
- Local review of incomplete or incorrect Blood Collection and Processing forms.
- Comparison of data from the Blood Collection and Processing Forms keyed locally with that keyed at the Central Laboratory.
- Reviewing the results from the laboratory testing to assure that collection, field processing, field storage and transport procedures are providing adequate samples for the test procedures, and long-term storage.
- Direct observation of collection, processing, storage and shipment procedures by the Quality Control Officer (or designee). The Quality Control Officer will review training procedures and directly observe collection and processing in the field no less frequently than each 3 months in the first 2 years of the project.

#### **5.2.4 ULTRASOUND EXAMINATION**

Ultrasound examinations will be carried out on each subject annually to diagnose thyroid abnormalities. The examinations will be conducted by certified MD ultrasonographers. The ultrasonographer will first, however, perform the thyroid palpation examination (see Section 5.2.5) and document palpation findings on the Palpation Examination Form.

#### 5.2.4.1 RATIONALE

The ultrasonographic examination will be used to characterize the entire thyroid gland and as a diagnostic test for abnormalities of the thyroid in terms of size and shape. It will be used to identify subjects with lesions that should be biopsied and will provide an analytic tool for investigating the pathogenesis of thyroid disease. Thermal print (TP) images of abnormal findings and magneto optical disks (MOD) for all images will provide documentation of findings and be used with quality assurance phantoms for quality control.

#### 5.2.4.2 EQUIPMENT AND SUPPLIES

The equipment and supplies needed for the ultrasound examination are as follows:

- Toshiba Imaging Equipment (Toshiba SSA-240 Ultrasound imaging system with 3.5 MHz linear array deep focus transducer, and 7.5 MHz Linear array -- or equivalent) at each location with 3M image buffer (MOD) and thermal printer device.
- 3M Kitecho Standoff No. 3520
- matrix printer, film and film development system
- sterile acoustic jelly
- QC phantoms
- thermal printer paper
- alcohol swabs
- cloth rolls or bolsters
- Ultrasound Examination Form
- ID labels

#### 5.2.4.3 TRAINING AND CERTIFICATION OF PERSONNEL

Five MD ultrasonographers will receive additional training for lengths of time dependent upon their prior experience and training. In order to conduct examinations for the study, certification will be required. Certification will be carried out by an experienced ultrasonographer based on ten consecutive ultrasound examinations performed on patients with a mix of ultrasonographic abnormalities and normal findings. Annual recertification will also be required.

After certification has been carried out, the names, dates and certification status of all examiners will be documented. This documentation will be kept on file at the data coordinating center. The data coordinating center will track the status of certification and advise individuals and the Director when recertification is required. In addition, once the ultrasound machines are purchased, there will be on-site training in use and care of the equipment by the manufacturer.

#### 5.2.4.4 INSTRUCTIONS FOR ULTRASOUND EXAMINATION

Each thyroid imaging study will be performed with the thyroid 7.5 MHz probe using acoustic jelly as the coupling media.

The subject will be examined supine, with neck extended by cloth roll or bolster. The examination will include evaluation of both lobes of the thyroid gland in transverse and sagittal projections, parathyroid glands (if identified) and superficial and deep cervical lymph nodes.

A series of standard images will be recorded on magneto optical disk (MOD) regardless of whether an abnormality is present or not. The views taken should be done in a standard order as follows:

1. Transverse scan of lower pole (right and left lobe)
2. Transverse scan of isthmus demonstrating as much of both right and left lobes as possible.
3. Transverse scan of upper pole (right and left lobe)
4. Sagittal scan of right lobe through the plane of the greatest cranio-caudal dimension.
5. Sagittal scan of left lobe through the plane of the greatest cranio-caudal dimension.

When abnormalities are noted, additional images will be obtained which delineate the lesion(s).

For subjects requiring evaluation of the parathyroid gland(s) (i.e., suspicion of parathyroid adenoma or history of hypercalcemia) particular attention should be directed posterior to the thyroid gland to detect any mass. Masses should be documented and measured in orthogonal planes. The carotid sheath, which includes the common carotid artery, internal jugular vein and deep cervical lymph nodes, should be imaged to document any enlarged lymph nodes.

The position of the transducer should be registered on all subject's images using the body mark system of the ultrasound device.

A series of standard measurements will be taken to determine thyroid volume as follows: anterior-posterior (a) and transverse (b) dimensions of each lobe on the largest transverse scan; the largest cranio-caudal (c) dimension of each lobe on the sagittal scan. Thyroid lobe volume calculations will be made based on the following formula:

$$V = 0.479 * a * b * c \text{ (cm}^3\text{)}$$

Total thyroid volume will be calculated as a sum of the right and left lobes. The isthmus volume should be taken into account if its anterior-posterior dimension is over 5 mm. The measurements of nodule volume will be performed in a manner similar to the lobe volume.

Thyroid volume will also be evaluated by comparison with the referent data taking into account sex and age. The result will be expressed in percent to the defined normal range. Percent will be calculated according to the formula:

$V$  of the subject/normal  $V$ , where normal  $V$  is an interval  $V_{\min}$ - $V_{\max}$  (100%). For example if the thyroid volume of the subject is increased the percent is calculated as  $V$  of the subject/ $V_{\max}$ . If the thyroid volume is decreased, it is calculated as  $V$  of the subject/ $V_{\min}$ .

Completion of the ultrasound examination will be documented on the Control Form and the subject sent to the next station.

#### 5.2.4.5 DATA COLLECTION AND TRANSFER TO DATA CENTER

Findings of the ultrasound examination will be recorded on the **Ultrasound Examination Form**. This form will be pre-labeled with the subject's ID number. The examiner (or his assistant) will record the instrument settings used for this subject along with the ultrasound findings using the data items and response categories provided on the form. See Appendix A-5-5 for the form and its specifications.

In addition, the data will be permanently recorded on the imaging system's magneto optical disk (MOD) and on temporary thermal prints. The thermal prints, each labeled with a subject ID label, will be attached to the Ultrasound Examination Form. If the patient is referred to the hospital, copies of the images showing the abnormality will be sent along to the hospital.

All files and documents must be labeled for identification purposes. Each MOD will be numbered along with the number of the ultrasound unit on which it is being used. The directory of studies will be established by the operator using software that will be provided with the system.

Within each exam (patient) there is the possibility of recording  $n$  images, the number of which can vary from patient to patient. In each image, the patient name, ID and other information (to be defined) will be entered from the keyboard, at the time the exam is conducted (*unless the ultrasound machine is equipped with a barcode reader*).

(NOTE 1: With an EPROM the manufacturer could provide to be inserted into the machine, the directory structure could be changed and simplified.)

The Ultrasound Examination form, thermal prints and MOD will initially be reviewed at the local center to determine if any findings require follow-up. The data form will be keyed locally by the data entry specialist. The MOD disks will be transferred to the data coordinating center for archiving, analysis and film preparation for selected cases. The prints taken in the field will stay with the subject's record.

#### 5.2.4.6 QUALITY CONTROL

A number of quality control procedures will be implemented to help ensure that the staff, equipment and examination procedures are performing to high standards.

##### 5.2.4.6.1 QUALITY CONTROL OF EXAMINERS

Quality control procedures for the ultrasound examination staff include the initial training and certification of examiners and annual recertification (see Section 5.2.4.3), direct observation of ultrasonographers, comparison of results obtained by different examiners and comparison of findings of the examiners with results of any referral examinations.

##### 5.2.4.6.2 QUALITY CONTROL FOR EQUIPMENT

The quality control protocol for the equipment is designed to establish that the system is working as expected. This includes the ability of the system to detect standard test objects, to resolve nearby structures, and to establish accuracy of the measurement "calipers." This is particularly important for field systems where boards in the system may be jarred loose in transport, transducers damaged, or other electronic damage incurred.

The following frequency of testing of the system will be carried out:

- **Mobile Stations** - Testing will be done each day that the system is moved. It will be performed at the new site before the first study subject is imaged.
- **Fixed Stations** - Testing will be done monthly and whenever there is a reason for concern.

The thyroid transducer used for thyroid imaging will be evaluated at the nominal operation gain settings with the ATS Model #550 Multipurpose Small Parts Phantom. Direct coupling of the transducer should be done through acoustic jelly. (Note: Since the velocity of sound is temperature dependent, it is important that the ultrasound test phantom be at room temperature for the caliper measurements to be accurate. If left outside (i.e., in a vehicle in the winter especially), it may take as long as 24 hours for the test object to return to standard sound velocity.)

Testing steps are as follows:

1. An image of the vertical-horizontal line targets should be made and recorded on MOD. The horizontal and vertical spacing should be recorded in the near and far field, and compared to previous measurements on

a log kept with the system. The lowest optimal gain settings should be used which get the best images of the targets as higher gain will broaden the appearance of the target size. (*Note: The final manual will include sample images of the kind that should be collected.*)

2. An image of the axial-lateral resolution arrays should be made and inspected to ascertain whether the system performance has changed in a noticeable manner. The same gain settings as noted in step 1 should be used.
3. An image of the cystic target structures should be recorded and viewed, to visually verify acceptable performance and recorded on MOD. These images should be recorded using standard preset imaging factors at each time, as these images are very gain dependent. All machines used on the project should use the same set of factors to permit inter-comparisons of system performance.
4. The same recording factors used in step 3 should be used to acquire and store images of the gray scale target structures.

The other ultrasound probes will be evaluated and dimensional and resolution properties verified on a less frequent, monthly basis, with the imaging procedures noted above.

If the conduct of these quality control measurements takes more than 15 minutes per day to accomplish, the target structure measurements may be performed on a weekly basis, or more frequently, when there is suspicion that device performance has changed. Images of test phantom response should be recorded on thermal prints (as well as MOD) whenever problems are encountered for communication with the service personnel who will need to be contacted to determine the cause of the problem, and to fix it. Depending on field experience with probe integrity, it may be necessary to have a spare linear probe with mobile systems.

The test data recorded on MOD will be returned to the data coordinating center at the end of each trip. A computer analysis of the quality control studies will be performed by the data coordinating center and results which indicate deteriorating performance will be reported to field teams as soon as possible following receipt of the MOD recorded data from the field. Depending of the severity of the problem, this would result in initiation of a request for a service call.

Hard copy prints of the abnormal studies can be generated on a postscript printer in the DCC. Photographs of the monitor screen may be made for slide presentations at meetings and for publication purposes. In subsequent years, a suitable photographic device can be attached to the workstation for this purpose. The acquisition of a video output board, such as the Radius video vision, on the PC used for MOD analyses would permit connecting a thermal printer that would permit generation of additional low cost, relatively high quality records for internal use. Since the original data are stored digitally, the impermanence of the thermal prints is not a serious problem.

Particular attention will need to be devoted to assessing and correcting for changes in caliper readings for gland size and nodule dimensions. Gland size calculations will be made based on maximum dimensions in each lobe sagittally and horizontally based on formula in current use (see Section 5.2.4.4), using the computer adjusted dimensions. In order to establish the relevant correction factors it will be necessary to identify relevant factors on the Ultrasound Examination Form.

#### 5.2.4.6.3 QUALITY CONTROL OF EXAMINATION FINDINGS

Initially, nodule size will be determined visually by a thyroid ultrasound expert viewing the computer data and delineating nodule borders manually. Staff of the data coordinating center will develop automated feature extraction methods using edge detection and texture analysis tools which duplicate the performance of the human expert. The computer based results will be entered into the subject's computer record. Periodic verification of the correspondence between human and computer entries will be made as part of the quality assurance program.

All images in which abnormalities have been noted will be reviewed at the designated referral center on a high quality workstation CRT monitor. Any differences in interpretation will then be noted and entered into the computer-based subject record. A sampling of allegedly normal records will be reviewed in a similar fashion as part of the quality control program of the field work. This will be done on a quarterly basis so that serious problems can be detected and corrected early and continuously throughout the study. The sampling should include all the ultrasound units, and all the different operators.

Hard copies of images of pathological findings in the thyroid will be printed out from the Silicon Graphics system.

Each MOD will have an identifier number assigned as described above, and the directory will identify the subject and his/her location on the disk. MOD disks will be archived for periods of active use, 3-6 months initially, at which time their contents will be transferred to DAT tape and CD-ROM for long-term archiving, and the MOD cartridges recycled to the field.

(Note: The computer systems in the DCC and in the ultrasound clinic area on which the MOD drive is mounted for data analysis needs also to be the one with the DAT tape for ease of image transfer.) Images will be transferred to the Silicon Graphics System for image analyses using CD ROMs prepared in the DCC. The DCC system will be used for Quality Assurance monitoring of the ultrasound devices.

#### 5.2.5 THYROID PALPATION EXAMINATION

Each subject will receive two thyroid palpation examinations. These examination will be performed by two examiners, one of whom will be the ultrasonographer. The examinations will be done to assess thyroid size and structural characteristics of the gland and adjacent neck structures. The ultrasonographer will do the palpation examination **before** doing the ultrasound.

#### 5.2.5.1 RATIONALE

The purpose of the palpation examination is to determine the size of the thyroid gland, the presence and location of structural changes in the thyroid gland and the presence and location of abnormal lymph nodes in the neck. The results will be used in conjunction with those obtained by ultrasound examination.

#### 5.2.5.2 EQUIPMENT AND SUPPLIES

Findings of the thyroid palpation examination will be recorded on the **Thyroid Palpation Examination Form**. No other equipment or supplies are needed for this examination.

#### 5.2.5.3 TRAINING AND CERTIFICATION OF PERSONNEL

The palpation examinations will be carried out by the endocrinologist and the ultrasonographer. A designated trainer-endocrinologist will train and certify all examiners working on the study. During the training period, the trainer will demonstrate the steps in inspection, palpation and recording of results as described below, will observe the trainee carrying out several such examinations and will correct any variations in technique.

For certification, the trainee will independently examine at least ten subjects, some with and some without thyroid abnormalities and will record the results. The trainee will be considered certified when he consistently obtains the same findings as the trainer. Recertifications will be required at intervals of one to two years.

The certifying endocrinologist will document the names, dates and certification status of all examiners tested. This documentation will be kept on file at the data coordinating center. The data coordinating center will track the status of certification and advise individuals and the Director when recertification is required.

#### 5.2.5.4 INSTRUCTIONS FOR THE THYROID PALPATION EXAMINATION

The examinations will be performed independently by the endocrinologist and the ultrasonographer. The ultrasonographer will not share the results of the ultrasound examination, or his palpation with the endocrinologist until the endocrinologist has completed his examination. A combined "final opinion" representing the consensus of the endocrinologist and the ultrasonographer will result from the individual examinations completed by the two examiners (see below Section 5.2.5.4.1).

Steps are as follows:

- Stand or seat the subject in front of the examiner in a good lateral light that accentuates the shadows of the normal structures. The entire neck should be visible down to the sternal notch (collars removed), with the examiner's eyes approximately at the level of the notch.
- Observe whether the gland is visible with the neck in the normal position or only when the neck is extended.
- Inspect the gland for any nodularity. If the gland is enlarged, determine whether it is visible from a distance.
- Palpate the gland initially from the front. First determine whether the trachea is in the midline at the sternal notch.
- Locate the isthmus just below the cricoid cartilage and gently palpate the thyroid lobes at each side of the isthmus using the thumbs or the fingers.
- Turn and flex the neck toward the side being examined while gently pushing on the thyroid cartilage from the opposite side.
- Repeat the palpation while the subject swallows. When necessary for better definition, repeat the palpation with the examiner behind the subject.
- Palpate the entire front of the neck, from the jaws to the clavicles, and the back of the neck for lymph nodes. The examiner may be in front or in back of the subject or in both locations.
- Record the findings of the examination on the Thyroid Examination Form.

##### 5.2.5.4.1 COMPARISON WITH ULTRASOUND

After the palpation results are recorded independently by the two examiners, the results will be disclosed and studied by the endocrinologist. Any discrepancies between the two examiners will be resolved by discussion and re-examination of the subject to reach consensus. Any discrepancies that remain unresolved will be handled as follows:

- A discrepancy between no enlargement of the thyroid and goiter grade IA or between goiter grade IA and grade IB will be registered to the **higher grade**.
- Discrepancies between the two examiners concerning patients with goiter grade IB and grade II or between a palpable nodule and negative findings should be reevaluated at the endocrinology clinic before the next visit.

The consensus achieved will be recorded as the diagnosis on the **Preliminary Summary of Medical Findings and Recommendations**.

When the endocrinologist's examination is completed, an indication will be made on the Control Form and all completed forms remaining for the subject will be held for pick-up by the data entry specialist.

#### 5.2.5.5 DATA COLLECTION AND TRANSFER TO DATA CENTER

Findings of the palpation examination will be recorded on the **Thyroid Palpation Examination Form**. For a standard examination, there will be two such forms completed, one by each of the two examiners. Appendix A-5-6 provides a copy of the form and specifications for its use. The endocrinologist will also complete the Preliminary Summary of Medical Findings and Recommendations which will indicate any diagnosis made and the need for referral in the judgement of the endocrinologist. All forms will be labeled with the subject's ID number and will be keyed locally into the study computer system.

#### 5.2.5.6 QUALITY CONTROL

Quality control procedures for the thyroid palpation examination will be implemented by the quality control officer and will include the following measures:

- Training and certification of examiners.
- Recertification of examiners on an annual or biannual basis.
- Conduct of each exam by two independent examiners.
- Evaluation of sources of variation in the keyed data.
- Direct observation of the examiners.

#### 5.2.5.7 PROVIDING RESULTS TO THE STUDY PARTICIPANT/EXIT PROCESS

After the specimen collection and thyroid examinations are completed, the endocrinologist will discuss initial findings with the subject (and his parents, if present) and provide a written copy of the **Preliminary Summary of Medical Findings and Recommendations** at that time or by mail. This form will be completed using information immediately available from the ultrasound and palpation. The subject will be informed as to whether he needs immediate referral to the hospital, a check-up in 3-6 months, repeat examination in one year or simply that the examiner is waiting for the laboratory results. A copy of the preliminary summary will remain in the subject's chart. The form and its instructions appear in Appendix A-5-7. The physician will answer any questions and clarify any information that the subject or his parents find unclear. The subject will also be told that a **Final Endocrinologic Summary and Recommendations** will be sent to his home and to his home polyclinic as soon as the results of the laboratory tests are available. Following this, the subject will be thanked for his participation and the visit will be concluded.

#### 5.2.5.8 PEDIATRIC/ADULT EXAMINATION

Following the thyroid examination, the subject will receive a general pediatric/adult examination and may be referred to the appropriate polyclinic or dispensary in the event of positive findings requiring further study. The pediatric/adult examination is not part of the research protocol.

#### 5.3 REPORTING RESULTS TO HOME POLYCLINIC

After laboratory test results are available, a copy of the **Final Endocrinologic Summary and Recommendations** will be mailed to the subject's home polyclinic. See Chapter 7 for more information.

#### 5.4 REFERRAL FOR FINE NEEDLE BIOPSY

Subjects with thyroid nodules or focal lesions of a specified size revealed by palpation or ultrasound examinations will be referred for fine needle biopsy.

##### 5.4.1 CRITERIA FOR REFERRAL

All thyroid nodules or focal lesions revealed by palpation or ultrasonography that are **1 cm or larger** at their greatest diameter will be referred for biopsy. In children under age 12, fine needle aspiration will be done on nodules **larger than 5 mm**. If diffusely altered echogenicity is present on ultrasonography, accompanied by one or more abnormal pretracheal, paratracheal, or parajugular lymph nodes not explainable by intercurrent disease, fine needle aspiration of the thyroid and one or more accessible nodes will be done.

##### 5.4.2 EQUIPMENT AND SUPPLIES

The following equipment and supplies are required for the fine needle biopsy or aspiration:

- Disposable syringe, one per puncture
- Pair of disposable gloves, one per puncture
- Disposable needle (25G), one per puncture
- Disinfective noniodine-containing spray suitable for ultrasound examination
- Microscope slides, 3-5 per puncture
- Spray-cyte

- Slide holders
- Staining solution and equipment
- Needle Biopsy Form

#### 5.4.3 TRAINING AND CERTIFICATION OF PERSONNEL

Fine needle biopsy will be done by an ultrasonographer under ultrasound guidance. For training purposes, the trainee will perform fine needle biopsy under the supervision of an expert on 12 patients. The trainee will be required to demonstrate the ability to obtain satisfactory specimens in >50% of cases.

#### 5.4.4 NEEDLE BIOPSY PROCEDURES

Fine needle biopsy will be performed only in a designated center, and may be done under ultrasound guidance. If identical multiple nodules are identified manually, all nodules will be biopsied..

Subjects may be prepared for the procedure by use of an oral tranquilizer. They will have the option of refusing the tranquilizer. The subject will be instructed to refrain from swallowing or talking during the procedure.

The subject will be in the supine position with a pillow placed under the shoulders in order to extend the neck and increase exposure of the gland. Local anaesthesia is not required. The skin will be prepared with a noniodine-containing antiseptic solution suitable for ultrasound examination.

The skin will be penetrated with a fine 25 gauge needle attached to a 10 ml syringe. A special device attached to the transducer of the ultrasound machine may be used. Sampling should be performed with short back and forth movements of the needle through the lesion. If the material does not appear in the needle hub, suction will be applied. The syringe plunger should be released, relieving the vacuum, before withdrawing the needle. Gentle pressure will be applied to the aspiration site to reduce the chance of hematoma formation.

The aspirated material will be transferred to glass slides pre-labeled with the subject's ID number. To prepare the slides, one or two drops of the aspirated material should be expressed onto a clean slide using the 1 cc of air previously drawn into the syringe. Then a second slide should be placed on top of the first slide and after the material spreads, the two slides should be pulled apart in a horizontal plane.

The slides should be air-dried or fixed by spray-cyte until staining with Giemsa. As each slide is prepared, it will be marked with a letter (A, B, C, etc) to indicate the site from which it was aspirated and the letter and corresponding site will be recorded on the **Needle Biopsy Form**.

Adequacy of the specimens will be immediately verified by the cytologist or endocrinologist himself. The smears should be considered to be adequate if a minimum of two slides demonstrate six to eight cell clusters. If the specimen is determined to be inadequate, another attempt will be undertaken. The maximum number of attempts per session is two per nodule. If the second attempt fails, depending on the endocrinologist's findings, the subject will be recalled in 3 to 6 months, or perhaps even referred for surgery if there are signs of metastases. At the next examination, fine needle biopsy will be repeated in subjects with persistent nodules in whom cytological findings were benign or indeterminate. In the presence of clinical features indicating disease progression, further management will depend on the clinical judgement of the endocrinologist.

The stained slides will be interpreted by the cytologist.

#### 5.4.5 POSSIBLE ADVERSE EVENTS FROM FINE NEEDLE BIOPSY

Possible adverse events resulting from the fine needle biopsy might include:

- pain
- fainting
- hysteria
- transient damage to the laryngeal nerve
- puncture of the trachea
- laryngospasm
- bleeding

If the trachea is entered during the procedure, the subject may cough and even produce blood-tinged mucus. In this situation, the procedure must be stopped and the subject should be observed by his physician. If the jugular vein or carotid artery is accidentally punctured, pressure should be applied to the site for several minutes to ensure that bleeding has stopped. In all cases, subjects will be handled according to standard medical practice. Every adverse event must be documented on the Fine Needle Biopsy Form.

#### 5.4.6 DATA COLLECTION AND TRANSFER TO DATA CENTER

Findings from the fine needle biopsy will be recorded on the **Needle Biopsy Form**. The form will be labeled with the subject's ID number. The form and its specifications appear in Appendix A-5-8. Completed Needle Biopsy Forms will be sent to the data coordinating center to be keyed there. Copies of these forms will be kept in the hospitals/clinics where the procedure was performed.

#### 5.4.7 QUALITY CONTROL

Quality control procedures for the fine needle biopsy include:

- Training and certification of physicians who perform the fine needle biopsy
- Review of subjects selected for procedure
- Direct observation of technique
- Quarterly review of all slides by at least one expert cytopathologist for adequacy and accuracy of diagnosis

## **5.5 DIAGNOSTIC OR THERAPEUTIC REFERRALS FOR OTHER THAN FINE NEEDLE BIOPSY**

### **5.5.1 THYROID REFERRALS TO THE DESIGNATED ENDOCRINOLOGICAL DEPARTMENT**

Subjects whose examinations reveal any of the following thyroid abnormalities will be referred to the designated Endocrinology Department.

#### **CLINICAL PRESENTATION/HISTORY:**

- all palpable thyroid nodules
- unexplained cervical lymph node enlargement (suspicious for tumor)
- clinical signs of functional abnormalities of the thyroid and/or parathyroid glands
- prior thyroid surgery patients with malignant disease should be referred to the hospital twice a year or any time new metastases are suspected
- prior thyroid surgery patients with benign diseases should be referred to the hospital annually or any time recurrence is suspected

#### **SONOGRAPHIC FINDINGS:**

- all nodules and focal lesions in thyroid gland on first detection
- nodules smaller than 5 mm perceived to increase in size under L-thyroxine treatment
- thyroid development abnormalities on first detection

#### **LABORATORY FINDINGS:**

- thyroid function tests TSH, which clearly support the diagnosis of hypothyroidism or hyperthyroidism by having two or all of the function tests outside the reference range and in the same "diagnostic" direction, or anti-thyroid antibodies with significantly elevated titres

In case of absolute refusal to be referred to the designated Endocrinology Department, subjects may be referred to specialists at the dispensaries or the local polyclinics.

### **5.5.2 THYROID REFERRALS FOR REPEAT EXAMINATION**

Subjects with any of the following findings will be requested to undergo a repeat examination in six months:

- thyroid nodules smaller than 5 mm in largest diameter after hospitalization
- diffuse moderate decrease of echogenicity
- a laboratory test of thyroid function which has a value outside the reference range after repeat testing or an antithyroid antibody test with a positive but low titre

### **5.5.3 OTHER ENDOCRINOLOGIC REFERRALS**

Other than for thyroid and parathyroid findings, endocrinologic referrals may be made (e.g., diabetes). Subjects may be referred to specialists at the local level. This will be left to the judgment of the endocrinologist performing the exam. Information regarding the condition and referral will be noted in the subject's regular medical record.

## **5.6 MEDICAL EMERGENCIES, ADVERSE EVENTS**

Subjects will be provided with immediate care for any medical emergency which may occur during their visits, whether or not it is related to study procedures.

Adverse events are defined as medical problems occurring as a direct consequence of a study procedure. The study examinations involve minimal risk. Adverse events will be handled according to standard medical practice. In addition, every adverse event not recorded on the appropriate specimen or examination form must be documented on an **Adverse Event Report** (Appendix A-5-9). This report will be sent to the chief endocrinologist, and will eventually be transferred to the data coordinating center. Review of these reports and adverse events reported on other data forms will be important in monitoring the integrity of the study.

## **6. LABORATORY DETERMINATIONS**

This chapter gives an overview of laboratory testing of urine and blood samples collected for the study and describes associated data flow. Detailed laboratory procedures, including equipment specifications and maintenance, assay protocols and quality control procedures are presented in a separate manual (see Master Laboratory Manual).

## 6.1 IODINE TESTING OF URINE

Iodine testing of urine will be performed for the subject when first screened.

Iodine testing requires an **isolated** laboratory, maintained iodine free with a fume hood and filtered ventilation. Detailed information on the testing protocol can be found in the Master Laboratory Manual.

### 6.1.1 DATA COLLECTION AND TRANSFER TO DATA CENTER

The urine assay data will be recorded on the Laboratory Results Form (or log) by sample ID number (see Appendix A-6-1). The data will be keyed at the Central Laboratory and the keyed data will be sent periodically to the data coordinating center to allow tracking of the test results and for quality control purposes.

## 6.2 THYROID FUNCTION TESTS

Thyroid function tests include TSH. Determination of TSH level will be used as a screening test for diagnosis of early hypothyroidism, occult hyperthyroidism and also in the followup of patients receiving suppression and replacement therapy by levothyroxine.

Details on the testing protocol are provided in the Master Laboratory Manual.

### 6.2.1 DATA COLLECTION AND TRANSFER TO DATA CENTER

The assay results for thyroid function tests will be visually scanned to determine that they fall within an acceptable range, using the procedures outlined in the Master Laboratory Manual. The chief of the Central Laboratory must sign all worksheets to indicate that the results have been reviewed. After this, the results will be reported, by sample ID, on the Laboratory Results Form (see Appendix A-6-1). The results will then be keyed and sent back to the examining center and to the data coordinating center. A hard copy will also be sent to the examining center. Results sent to the examining center will be reviewed by the endocrinologist and used for completion of the Final Endocrinological Summary and Recommendations. Results sent to the data coordinating center will allow the data coordinating center to track test results and perform appropriate quality control functions.

## 6.3 OTHER BLOOD TESTS

Anti-thyroid antibody tests include anti-TPO.

Details of the testing protocols are provided in the Master Laboratory Manual.

### 6.3.1 DATA COLLECTION AND TRANSFER TO DATA CENTER

The assay results will be reviewed to determine that they fall within an acceptable range, using the procedures outlined in the Master Laboratory Manual. The chief of the Central Laboratory must sign all worksheets to indicate that the results have been reviewed. After this, the results will be reported, by sample ID, on the Laboratory Results Form (see Appendix A-6-1).

The results will then be keyed and sent to the examining center and to the data coordinating center. A hard copy will also be sent to the examining center. Results sent to the examining center will be reviewed by the endocrinologist and used for completion of the Final Endocrinological Summary and Recommendations. Results sent to the data coordinating center will allow the data coordinating center to track test results and perform quality control functions.

## 6.4 LABORATORY SUMMARY FOR THE ENDOCRINOLOGIST

Having completed his physical examination and his **Preliminary Endocrinologic Summary and Recommendations** at the time of the participant's visit, the endocrinologist will review the laboratory results in order to complete the **Final Endocrinologic Summary and Recommendations** (see Appendix A-7-1).

Laboratory results will be received via computer file and hard copy from the Central Laboratory. After the results are used to complete the Final Endocrinology Summary and Recommendations form, a copy will be sent to the local polyclinic of the subject and another copy will be filed in the medical record maintained by the study for that participant.

## 6.5 LONG-TERM STORAGE OF SPECIMENS

All blood specimens will be stored for three months at  $-20^{\circ}\text{C}$ . Abnormal bloods or those of subjects with endocrinologic findings will be stored for one year (or longer) at  $-55^{\circ}\text{C}$  or lower.

# 7. FINAL ENDOCRINOLOGIC SUMMARY AND RECOMMENDATIONS

With the completion of the endocrinologic examination, and the final laboratory results in hand, the endocrinologist will prepare the **Final Endocrinologic Summary and Recommendations**. Note that this form is prepared before any biopsy, surgical, or pathology results are available. The Final Endocrinologic Summary and Recommendations will include any preliminary diagnoses and the endocrinologist's recommendations for follow-up and/or treatment. The Final Endocrinologic Summary and Recommendations and specifications for completion of this form are shown in Appendix A-5-10.

## 8. ENDPOINT DETERMINATION AND COHORT FOLLOW-UP

### 8.1 DIAGNOSIS OF THYROID AND PARATHYROID PATHOLOGY

The nodular and diffuse thyroid lesions revealed after clinical examination and laboratory tests will be additionally analysed in order to diagnose thyroid cancer and other thyroid diseases. The diagnosis of benign and malignant thyroid disease at the preoperative period will be established at the Clinical Endocrinological Department, and after surgical treatment it will be verified on histological specimens at the Pathology Laboratory of the Institute of Endocrinology.

#### 8.1.1 HISTOLOGICAL EXAMINATION

##### 8.1.1.1 INTRAOPERATIVE HISTOLOGICAL EXAMINATION OF BIOPSY MATERIAL USING FROZEN SECTIONS

In the presence of nodular lesions or focal infiltrations of thyroid gland, enlarged cervical lymph nodes, the lesioned thyroid lobe (or its part), the enlarged lymph nodes revealed may be, immediately after surgical ablation, sent to the Laboratory of Morphology for express-diagnostic histological examination. Such an examination is of paramount importance in case of unclear cytologic conclusions with smears obtained as a result of fine-needle aspiration biopsy.

After measuring length, width and thickness of the preparation, the lobe removed or its part must be consecutively cut into slices 4 - 5 mm thick, the maximum diameter of nodules or focal dense areas has to be measured and presence of capsule, capsular invasion, cystic or hemorrhagic foci, etc., is noted.

The lymph nodes removed should be also measured and cut into slices with indication of presence of infiltrated areas, hemorrhages, cysts, etc.

One of thyroid tissue fragments obtained with nodule or focal dense areas as well as one of the fragments of a removed lymph node are placed on specimen discs covered with tissue freezing medium, are frozen with Cryospray and put into the Cryostat. The frozen sections obtained by cryomicrotomy 12 to 15 mcm thick are carried to microscope slides marked with ID number of patient with an additional mark of specimen location (figures 1,2,3, etc.), are quickly fixed in 96 % ethanol, stained using a fast technique with hematoxylin and eosin, and then they are examined by a pathologist at light microscope.

All the procedure from the moment of biopsies' delivery to the Pathology Laboratory till the communication of the results ( by phone) to the Surgery Department of the Institute of Endocrinology takes on the average 15 to 30 minutes depending on the number of biopsies sent for express-analysis and the necessary quantity of sections for making a provisional diagnosis.

In order to carry out intraoperative histological express-analysis the following equipment, supplies and reagents are necessary:

- cryostat (freezing microtome);
- microscope;
- disposable gloves;
- tweezers of different size;
- a table for biopsies' preparation;
- disposable blades for biopsies' preparation;
- specimen discs of different surface;
- tissue freezing medium;
- Cryospray;
- disposable blades for Cryostat;
- holders for microscope slides;
- histological glass dishes;
- ethanol;
- xylene;
- hematoxylin solution;
- eosin solution;
- microscope slides;
- coverslips;
- frozen tissue embedding media;

- Pathology Form for histological express-analysis;

### 8.1.1.2 POSTOPERATIVE HISTOLOGICAL EXAMINATION OF BIOPSY MATERIAL

After completing surgery, all removed material is sent to the Pathology Laboratory. After describing the macrospecimens, the specimens delivered will be cut into slices (see 8.1.1.1) fulfilling the measurements given in the Pathology Form: dimensions of lobe, thyroid nodules, infiltrations, cysts, lymph nodes (if available).

The following number of specimens is to be selected for further histological processing:

- in case of diffuse thyroid lesion: 2 to 3 fragments from different lobe areas;
- in case of solitary nodule: all the fragments obtained of nodule tissue (for a nodule up to 2 cm diameter) or 5 to 6 fragments from different nodule areas (for a nodule more than 2 cm diameter), as well as 2 to 3 fragments of extranodular thyroid tissue;
- in case of multinodular lesion: 2 to 3 fragments of each nodule and 2 to 3 fragments of extranodular tissue;
- all the lymph nodes removed.

The specimens obtained are put in plastic cassettes marked with ID number of patient with additional mark of specimen locations (figures 1, 2, 3, etc.), they are fixed in 10 % neutral formalin, dehydrated in ethanol of increasing concentrations, cleared up in three xylene portions, impregnated with in three paraffin portions (one of them is supplied with a vacuum attachment, and embedded into paraffin. All the procedure of histological processing of specimens is carried out under standard conditions in corresponding tissue processors and embedding centers.

From each of the paraffin blocks obtained, sections 4 to 5 mcm thick (2 to 4 sections depending on the features of the specimen delivered) are obtained on a microtome, these sections are carried to a special water bath, and then to microscope slides. After drying, the preparations are deparaffined in two xylene portions and stained with hematoxylin and eosin using a standard technique in the staining machine. After embedding in Eukit histological mountant, the specimens will be analysed by a pathologist at light microscope (in complicated cases or when verifying diagnosis of thyroid carcinoma, the preparations will be studied by two pathologists).

In order to carry out postoperative histological examination, the following basic equipment, supplies and reagents are necessary:

- tissue processor;
- vacuum unit;
- embedding center;
- microtome;
- water bath;
- staining machine;
- microscope;
- disposable gloves;
- tweezers of different size;
- table for biopsies' preparation;
- disposable blades for biopsies' preparation;
- dishes for preliminary fixation of biopsy material;
- 10 % neutral formalin;
- ethanol;
- xylene;
- hematoxylin solution;
- eosin solution;
- paraffin;
- disposable blades for microtome;
- holders for microscope slides;
- histological glass dishes;
- microscope slides;
- coverslips;
- Eukit histological mountant;
- Pathology Form for postoperative biopsy material analysis;
- computer with line supply.

As far as possible (availability of reagents), biopsy material will be also fixed and processed in order to carry out further electron microscopic examination.

### 8.1.1.3 DATA COLLECTION AND TRANSFERRING TO DATA COORDINATION CENTER

The results of histological examination have to be entered in a Pathology Form which will be marked with ID number of patient. This Form is given in Appendix A..... The Forms filled in will be sent to the Data

Coordination Center (and transmitted through computer modem communication). Duplicates of these Forms will be also stored at the Pathology Laboratory (on paper and floppy disks).

#### **8.1.1.4 QUALITY CONTROL**

- training of laboratory assistants-histologists performing histological processing of biopsy material, microtomy and staining of preparations;
- training of pathologists involved in verification of diagnoses;
- realization of additional methods of investigation in complicated cases of differential diagnosis: immunohistochemical study with antibodies against thyroglobulin and calcitonin when suspecting a medullary or anaplastic carcinoma; immunohistochemical study with antibodies against Common LA when suspecting a thyroid lymphoma; histochemical study for elastic fibers or immunohistochemical study with antibodies against endothelial cells in order to evidence vascular invasion in case of follicular carcinoma;
- realization of additional examination of histological preparations by leading experts-pathologists;
- creation of special archives of paraffin blocks and histological specimens (minimum quantity: one block and one histological specimens from each nodule or tumoral focus, area of extranodular or extratumoral thyroid tissue, metastatically lesioned lymph node). The experts-pathologists will be provided with archives preparations, if necessary, paraffin blocks may be used for carrying out extended morphological studies, for example, using immunohistochemistry and in situ hybridization methods.

#### **8.1.2 DIAGNOSTIC CRITERIA**

##### **THYROID CANCER:**

The diagnosis of thyroid cancer should be based on the final histology conclusion after thyroid surgery.

As described in Section 5.4, fine needle biopsy will be performed on all palpable nodules and/or focal lesions identified on ultrasound that are 1 cm or larger in greatest diameter in subjects age 12 or older and larger than 5 mm in subjects under age 12 and in patients with diffusely altered echogenicity accompanied by deep cervical lymph node enlargement. If the cytologic diagnosis is "malignant" or "suspicious," surgical excision and histology examination will be undertaken.

An elevated serum level of thyroglobulin is considered suspicious for metastatic thyroid cancer. Subjects with this laboratory result will undergo additional diagnostic procedures to rule out lung and bone metastases. The thyroid gland will also be reexamined by an expert sonographer. Even with only a slight suspicion of malignancy, surgery and histological examination will be performed, or alternatively, the subject will be put on a suppressive dose of levothyroxine and followed at 3 to 6 month intervals.

##### **NODULAR GOITER:**

The diagnosis of nodular goiter should be based on clinical findings of any size thyroid nodule confirmed by ultrasound examination and proved to be benign by fine needle biopsy in nodules of the size indicated above. After fine needle biopsy, the diagnosis should be defined by cytologic findings as neoplastic, e.g. possible adenoma or carcinoma, or non-neoplastic, e.g. colloid nodule or cyst.

Subjects with a benign diagnosis on fine needle biopsy or with focal lesions smaller than indicated above, may be placed on thyroid hormone therapy (approximately 2.5 mg/kg levothyroxine per kg of body weight) and followed for 6 months. If the lesion increases in size, the fine needle biopsy will be repeated and the necessity for surgical treatment will be evaluated by the endocrinologist and the surgeon.

##### **HYPOTHYROIDISM:**

An elevated TSH combined with lowered T4 or FT4 is diagnostic of hypothyroidism and treatment will be instituted. Mild elevations of TSH only suggests subclinical hypothyroidism. These subjects will be followed closely, with repeat examinations every 6 months.

##### **AUTOIMMUNE THYROIDITIS:**

An elevated level of ATPO and/or ATG is suggestive of autoimmune thyroiditis. For a final diagnosis, the ultrasound findings i.e., hypo-, hyperplasia, low echogenicity, will be taken into consideration as well as tests of thyroid function. Serum obtained during the screening examination will be used to measure ATPO. Serum positive for ATPO will be stored for reevaluation and determination of ATG.

##### **HYPERPARATHYROIDISM:**

An elevated PTH level indicates hyperparathyroidism. Serum will be used to measure calcium and albumin. Serum of subjects with hypercalcemia will be stored for immunoassay of PTH.

##### **ENDEMIC GOITER:**

Clinical or ultrasound findings of enlarged thyroid gland in an euthyroid or hypothyroid subject with normal or subnormal levels of ATPO living in an iodine-deficient area indicates endemic goiter.

Treatment-induced pathology must be diagnosed and includes:

#### **HYPOPARATHYROIDISM:**

A decreased level of calcium or clinical features of hypocalcemia in post-operative patients indicates hypoparathyroidism.

#### **LARYNGEAL NERVE DAMAGE:**

This diagnosis will be based on clinical findings (e.g. hoarseness, stridor) and laryngoscopy.

### **8.2 SUBJECT HOSPITALIZATION OTHER THAN STUDY REFERRAL**

Hospitalizations will be tracked primarily to identify those related to thyroid and parathyroid disease, both prospectively and retrospectively. For subjects undergoing additional diagnostic evaluation and treatment as a result of study examination, study staff will have knowledge of the details of the hospitalization (see above). All other subjects will be questioned during the interview part of the examination visit about any hospitalizations in the past. In the baseline year, this will include all prior hospitalizations. At each annual visit, it will include hospitalizations in the past year. If the hospitalization was related to a thyroid problem or there is any suspicion that the hospitalization was related to a thyroid problem, the medical records from that hospitalization must be obtained for review. The data coordinating center may be involved in the procurement of these medical records. Tests performed, surgical procedures and diagnoses will be abstracted onto the **Hospitalization Abstract Form** by the endocrinologist assigned to the subject when such records are available. Records available only elsewhere will be abstracted by personnel of the epidemiology group and reviewed by the study endocrinologist. The Hospitalization Abstract Form and instructions for its completion are shown in Appendix A-8-1.

Once completed, the form will be sent to the data coordinating center for processing. A copy will also be sent to the subject's home polyclinic.

### **8.3 DEATH**

All deaths occurring among members of the study cohort will be identified and the cause of death will be determined by review of the death and medical records. The aforementioned review of death and medical records will be carried out by the personnel of the epidemiology group. The data will be keyed at the data coordinating center and the abstracts filed in the subjects charts.

#### **8.3.1 NOTIFICATION OF STUDY OF SUBJECT DEATH**

Deaths will be ascertained in a number of ways.

These include:

- Notification by the family. This may happen in response to the letter sent to the subject to schedule an appointment.
- Follow-up of thyroid cancers diagnosed as part of the study procedures.
- Notification from the local polyclinic. Each polyclinic will be provided with a list of subjects in its jurisdiction and asked to notify the study in the event of death. These lists will be updated annually to reflect address changes.
- Periodic linkage with the Chernobyl Registry.
- Review of computerized file of deaths. Assuming such a file becomes available for Ukraine, this file will be linked to the study cohort file periodically to ascertain deaths.

#### **8.3.2 OBTAINING PERTINENT RECORDS**

For each study subject who dies during the course of the study, information regarding the cause of death will be obtained. First, the death certificate will be obtained. If the subject died of disease, a copy of any terminal hospital record will be obtained for review. If an autopsy has been performed, and thyroid tissue retained, it will be important to obtain a block of thyroid tissue. Thyroid tissue will be sought regardless of cause of death.

If death is in any way related to thyroid disease, to any treatment for thyroid disease, or to metastasis from a primary thyroid cancer, full clinical details will be sought from any hospitals where the subject was treated, and will be documented on the **Death Data Form** (see Appendix A-8-3 for the form and its specifications).

#### **8.3.3 EXPERT REVIEW OF DEATH DATA**

At periodic intervals, files on deaths occurring in that interval will be reviewed by an expert group appointed by the director and representing relevant medical specialties including endocrinology, surgery, pathology and internal medicine.

## **9. DATA MANAGEMENT**

This chapter describes data management activities for the study. It includes an overview of the role of each participating organization in data management, presents software and forms to be utilized and discusses data processing and reporting functions. Detailed specifications for data management and data processing systems are provided in a separate manual entitled, Data Management Manual.

### **9.1 OVERVIEW OF DATA FLOW**

Data for the study will be collected on paper forms with codes designed for ease of computer entry and many of which will then be keyed into the computer at the location where the examination is performed. Computer entry should be accomplished whenever possible while the subject is still in the area so that ambiguous entries may be clarified before computer entry. Following quality control checks, the paper records of the visit will usually be filed at the place where examinations are performed, and to which the mobile units are attached. Laboratory test results will generally be keyed and filed at the Central Laboratory.

Once the data have been entered into the computer and adequately verified (see Section 9.3), they will be transmitted to the Data Coordinating Center by means of weekly mailings of diskettes. Later in the life of the study, data transfer from places of examination may be accomplished by telephone lines and modems.

Paper files will be kept in locked files or locked areas and in study-number sequence. Computer files will be accessed only by passwords issued to those with a "need to know" by the authority of the Project Director.

#### **9.1.1 STAFF RESPONSIBILITIES FOR DATA MANAGEMENT**

Outlined below are the data management responsibilities of the Data Coordinating Center, the fixed examination centers, the mobile units, the Central Laboratory and the Epidemiology Group.

##### **RESPONSIBILITIES OF THE DATA COORDINATING CENTER**

- Establishment of the cohort
- Training the staff to work with PC
- accession the selection made by the dosimetry group
- update individual records with identifying information from other sources
- update file with tracing efforts and their results
- Allocation of subsamples of the cohort to examining groups on geographical basis
- Design systems for specimen identification and for identification of data collection and other forms
- Make appointments with study subjects
- Print and mail contact and appointment letters
- reschedule appointments as necessary
- prepare registration logs for examining teams
- Design and prepare forms, labels, and other study materials
- design bar-code system
- prepare and distribute data collection and management forms
- design, print and distribute subject ID and specimen labels
- entry of forms not keyed by examining units
- repeat entry of forms keyed at examining units for quality control checks

##### **QUALITY CONTROL OF THE FOLLOWING ACTIVITIES:**

- editing, coding and data entry
- shipment of specimens and data collection forms
- inventory subsystem
- ultrasound images
- referral of specimens to outside laboratories

##### **CONTROL OF STAFF CERTIFICATION**

##### **TRACK DELIVERY AND DISTRIBUTION OF EQUIPMENT**

##### **REPORT ON THE PROGRESS OF THE STUDY:**

- provide and maintain an automated study management system for use by the examination centers
- prepare and distribute reports from the study management system
- track laboratory specimens

**COMPILE AND MAINTAIN THE STUDY DATABASE:**

- provide and maintain coding, keying, editing and data backup specifications and programs to the examination centers
- handle incoming data from the examination centers
- review coding/keying/editing decisions made by the examination centers and ensure consistency across the centers
- act as the prime contact for data-related issues and technical questions
- provide support for statistical and clinical requests

**RESPONSIBILITIES OF THE EXAMINATION CENTERS****HANDLE LAST-MINUTE CHANGES IN APPOINTMENTS WITH STUDY SUBJECTS****MANAGE THE PAPER FLOW FROM STUDY VISITS:**

- prepare/update locator forms with subject contact information
- code and key completed data forms
- edit keyed data using programs developed by the Data Coordinating Center
- send the coding/keying decision log to the Data Coordinating Center on a monthly basis for review
- organize weekly mailings of study data to the Data Coordinating Center
- file medical records generated by the study

**TRACK SPECIMEN COLLECTION, PROCESSING AND SHIPMENT:**

- key completed specimen forms and ship forms and specimens to the Central Laboratory
- enter specimen tracking information into the database
- run specimen check programs and resolve discrepancies
- generate transmittals to accompany the shipment of specimens and send the transmittals, along with the samples, to the Central Laboratory

**TRACK SUBJECT PARTICIPATION STATUS:**

- maintain registration logs
- complete and update, as necessary the Locator Form, Missing Data Form and Non-response Form
- enter participation status information into the study management system

**RESPONSIBILITIES OF THE MOBILE UNITS****MANAGE THE PAPER FLOW FROM STUDY VISITS:**

- code and key completed data forms
- prepare/update locator forms with subject contact information
- edit keyed data using programs developed by the data coordinating center
- return study data to the fixed examination center to which the mobile unit is attached for filing and transmittal to the data coordinating center

**TRACK SPECIMEN COLLECTION, PROCESSING AND SHIPMENT:**

- key completed specimen forms
- enter specimen tracking information into the database
- run specimen check programs and resolve discrepancies
- return specimen forms and samples to the fixed examination center to which the mobile unit is attached for shipment to the Central Laboratory

**TRACK SUBJECT PARTICIPATION STATUS:**

- maintain registration logs
- complete and update, as necessary the Locator Form, Missing Data Form and Non-response Form
- enter participation status information into the study management system

**RESPONSIBILITIES OF THE CENTRAL LABORATORY**

## RECEIVE BLOOD AND URINE SAMPLES, FORMS AND TRANSMITTAL LOGS

## ENTER SPECIMEN TRACKING INFORMATION INTO DATABASE

## RECORD TEST RESULTS ON LABORATORY RESULTS FORMS AND KEY INTO STUDY COMPUTER SYSTEM

## INVENTORY CONTROL OF LABORATORY SUPPLIES AND EQUIPMENT

### RESPONSIBILITIES OF THE EPIDEMIOLOGY GROUP

#### ESTABLISHMENT OF THE COHORT:

- cooperate with the data coordinating center in obtaining identifying information
- plan and carry out tracing efforts to locate subjects
- collecting information on death events.
- to coordinate work with local medical clinics.
- to coordinate work with non-response cases
- define parameters for Cohort Selection
- collect information on hospitalisation

#### FOLLOW-UP WORK

- on non response
- on migrants

#### OTHER FUNCTIONS

- reporting
- analysis

#### 9.1.2 QUALITY CONTROL FOR DATA MANAGEMENT

Quality control will be exercised by the data coordinating center and the Central Laboratory on the basis of statistical analyses of the individual operations and of their inter-relationships. In addition, certain operations may be repeated, and double-keying will be practiced, at least initially in order to establish error rates. Further details of the data management quality control plan are provided in subsequent sections of this chapter.

### 9.2 FORMS AND SOFTWARE

#### 9.2.1 FORMS

There are two types of forms used for the study: management forms and data collection forms. Management forms are used to document and support administrative aspects of the study. Data collection forms are used to record information collected from and about individual study participants. The specific forms, their use and disposition are described below. A form manual will be prepared and maintained.

**Management forms:** These are forms which provide information for the management of study activities.

- A **consent/assent form** will be used to document that the subject has agreed to participate in the study. It will be signed by the nurse or interviewer who administers it. It will be filed in the subject's study file at the local center. Appendix B-5-1.
- The **Locator Form** will be used to record identifying and tracking information about the subject. Information on this form will assist the Epidemiology group in finding the subject in subsequent years of the study. It will be keyed into the study management system at the data coordinating center and updates will be sent to the data coordinating center by the examining centers as they are obtained. Appendix B-5-2.
- The **registration log** will be maintained at the registration desk to record the flow of subjects for examination, missed appointments, arrivals prior to appointment, etc. This log will be generated by the data coordinating center as it is responsible for appointment scheduling. After completion, it will be returned to the data coordinating center so that action can be taken on missed appointments and other non-response situations. Appendix B-5-3.
- The **control form** carried by the subject from station to station and on which the fact of examination at each station is recorded. It will contain the reason why any examination was not performed. This form is

left at the final station when the subject has completed all examinations. It will be keyed and filed at the local examination center and the data sent to the data coordinating center. Appendix B-5-4.

- **Transmittal forms** will accompany shipments of urine and blood samples to the testing laboratories. These forms will indicate the date and contents of the shipment. Information from the transmittal will be entered into the study management system at the local examination center and at the Central Laboratory and sent to the data coordinating center so that samples can be tracked. Appendix B-5-5.
- A **nonresponse form** will be completed by the data coordinating center, medical support facility or epidemiology group to document information about a subject who will not be participating in a particular year or a subject who is lost to follow-up, or told that he/she refuses to participate at all, or if he/she didn't show up in appointment time. This form will be keyed into the study management system at the data coordinating center. Appendix B-9-1.

Data collection forms: These are the forms on which the study data will be entered. They include:

- The **initial abstract form** on which is recorded basic demographic, relevant medical and identifying information about the study subject collected as the cohort is assembled. Information on this form will be keyed and compiled by the data coordinating center. Appendix A-3-1.
- The **initial interview form** on which is recorded prior medical history and exposure information useful for dosimetry. This form will be keyed at the local examination center (*or epidemiology group or data coordinating center? - and filed where?*). Appendix A-5-1.
- The **annual interview form** on which is recorded information about health events occurring in the past year. This form will be keyed locally and filed there. Appendix A-5-2.
- The **urine collection and processing form** to record the fact of the collection, any reason for inadequacy or absence of the sample, and the subsequent processing and shipment of samples to the Central Laboratory. This form will be filed at the local examination center and transferred to the DCC. Appendix A-5-3.
- The **blood collection and processing form** to record the fact of the collection, any problems, and the subsequent processing, storage and shipment to the Central Laboratory. This form also moves with the collected specimen to the Central Laboratory. It will be keyed and filed at the local examination center and transferred to the DCC. Appendix A-5-4.
- The **ultrasound examination form** on which will be recorded the findings of this examination. In addition, images will be recorded into computer files and transferred to the study computer. The form will be keyed and filed at the local examination center. Appendix A-5-5.
- The **thyroid palpation form** will be used to record the results of the ultrasonographer's and endocrinologist's examination of the thyroid and the surrounding area. This form will be keyed and filed at the local examination center. Appendix A-5-6.
- The **Preliminary Summary of Medical Findings and Recommendations** which will be given to the subject at the end of the visit to summarize the medical findings and provide any necessary recommendations. This form will be keyed at the local examination center. A copy of this summary will be filed in the subject's chart. Appendix A-5-7.
- The **adverse event report** will document adverse medical events, not reported on an examination data form, which result from a study examination/procedure and/or occur during a visit to the examination center. Appendix A-5-9.
- The **laboratory results forms** on which the Central Laboratory will enter the results of the various tests prescribed by the research protocol for both urine and blood. These may be paper forms or computer files. If paper, they will be keyed at the Central Laboratory. Data files will then be sent to the appropriate local examination center and the data coordinating center. Appendix A-6-1.
- The **Final Endocrinologic Summary and Recommendations** which is completed by the endocrinologist after the laboratory results are received and summarizes the final findings and recommendations of the examination and testing. It will be keyed at the local examination center. Copies will go to the subject, the subject's home polyclinic and to any referral facility. A copy of this summary will also be filed in the subject's chart. Appendix A-7-1.
- The **needle biopsy form** on which will appear the indications for biopsy, when, how, and by whom biopsy was performed, information about the initial evaluation of the sample, and the results of the cytologic examination. This form will be keyed (*at the data coordinating center?*) and later filed in the subject's chart. Appendix A-5-8.
- The **pathology form** will be used to record the pathologic diagnosis of thyroid disease. It will be completed by the study pathologist and sent to the data coordinating center to be keyed. A copy will be filed in the subject's record. Appendix A-8-1.
- The **hospitalization abstract form** will be used to record non-study hospitalizations related to thyroid conditions. This form will be completed by the epidemiology group and reviewed by the study endocrinologist. It will be keyed by the epidemiology group and the data sent to the data coordinating center. The form will be filed in the subject's record. Appendix A-8-2.

- The **death data form**-which will provide information of the date and causes of death for a participant who dies during the course of the study. It will be completed by and keyed by staff of the epidemiology group. The form will be filed in the subject's chart. Appendix A-8-3.

### 9.2.1.1 QUALITY CONTROL FOR STUDY FORMS

Measures will be taken at each step in the handling of study data forms to ensure that the data are of high quality. These measures include:

- Double keying, at least initially, to establish error rates.
- Computer edits for missing forms, for completeness or recorded information, for internal consistency, for consistency with research protocol requirements, and for consistency with other information in the database.
- Independent expert review of form content, e.g., the death data form.

### 9.2.2 SOFTWARE

Software systems will be developed by the data coordinating center to support the management of the study and the processing of the data collected. The management system will be used to track the participation status of subjects throughout the course of the study. It will indicate whether or not the subject has completed the examination components in a particular year of the study, whether the subject is deceased, whether he is lost to follow-up, etc. The management system will be used to generate progress reports to assist project staff in monitoring the study. Software for processing the study data will include keying, editing and updating components. Computer edits will be used to check the data for internal consistency, completeness, acceptable codes, etc..

The data processing systems utilized for the study will make use of the following software packages:

- MS DOS 6.21
- NetWare 4.1
- MS Windows 95, NT 4.0
- Delphi 2.0 Client-Server
- Oracle(Interbase)

## 9.3 PROCESSING OF STUDY DATA

Processing study data, that is, data from all the data collection forms and some of the management forms listed in Section 9.2.1, includes manual editing, coding, keying and computer editing. These procedures are detailed in this section.

### 9.3.1 MANUAL EDIT

Before the data forms are keyed into the computer they must be scanned for completeness, presence of written comments that will require codes, illegible entries, etc. This will be done by the data entry specialist as soon as possible. If problems are found which require it, the form should be returned to the person who completed it for correction. Manual editing should be done relatively quickly; a minimal delay before keying is desirable.

### 9.3.2 CODING

Coding is the process of assigning a numeric value to a response. To the extent possible, items on the data collection forms will be precoded, that is, they will have numeric codes already assigned on the data form. However, on some forms there may be a few items which require coding after the form is completed. These items include residential information on the interview, diseases and responses in which the answer given does not fit into existing precoded categories. (See Section 9.3.2.2 and 9.3.2.4 below.) Detailed item-by-item coding specifications will be prepared for every data form.

The data entry specialist will be responsible for coding these items. All codes assigned must be documented in a **Coding Decision Log**. Since coding will be done in more than one location and over an extended period of time, it is important that consistent decisions be made within and across the centers about how items are coded. Therefore, the coding decision log will be routed through the Data Coordinating Center for review. Decisions which are reviewed and approved by the Data Coordinating Center must be dated and distributed periodically to every location and entered into the Coding Decision Log for future reference. For consistency, this should be done in such a way that all locations receive the information at the same time.

#### 9.3.2.1 GENERAL CODING GUIDELINES

The following are general guidelines for coding open-ended items and also apply to items in which the respondent has not entered their answer in a pre-existing category and the answer needs to be coded.

- Code the forms in a different color pen from the one used to complete the form (red is suggested).
- Whenever boxes are provided for an entry, the information should be right-justified and any unused boxes on the left filled with zeros (0's). ("Right-justified" means that the last digit of the number to be entered is written in the right-most box.)

Example: if there are 4 boxes available to enter the value '781', the value would be entered as:

0	7	8	1
---	---	---	---

- Enter one character in each box. Round values after a decimal point to fit in the boxes provided. When rounding off a decimal, use the following rule. If the last digit is between 1 and 4, drop the last digit. If the last digit is between 6 and 9, add one to the preceding digit. Rounding the value "29.3" would give "29," while rounding the value "29.7" would give "30." If the last digit is 5, round up if the preceding digit is odd and round down if the preceding digit is even. Never add boxes. Never add new decimal points. Never move decimal points.

Example: There are 4 boxes, with one box to the right of the decimal point (shown below). The value '385.67' would be entered as:

3	8	5	.	7
---	---	---	---	---

Example: There are 4 boxes, without a decimal point. The value '385.67' would be filled is as:

0	3	8	6
---	---	---	---

- If the value is too large to fit correctly in the boxes provided, fill in the right-most box with an '8' and fill in the rest of the boxes with "9's." Then write the actual value in the right-hand margin of the page.

Example: There are 4 boxes, two to the right of the decimal point. The value '385.67' would be entered as:

9	9	.	9	8
---	---	---	---	---

385.67

- Dates - the last two digits of the year go in the last 2 boxes, the number of the month goes in the second 2 boxes, and the number of the day goes in the first 2 boxes.

For example, if the date to be entered is July 17, 1987, the correct way to fill in the date is:

1	7	0	7	8	7
---	---	---	---	---	---

When there is only one digit to go in the 2 boxes that are allowed, that digit goes in the second box and the first box is filled in with a '0'. If any part of the date is unknown, enter '--' in its place to indicate this.

- If an item of information is missing and cannot be obtained, the boxes for that item should be filled with "9's."
- If the item is from a questionnaire and the participant refused to give the information, the boxes for that item should be filled with "9997."

### 9.3.3 KEYING

Data entry will be done in duplicate by independent data-entry clerks and compared by means of special software. Discrepancies will be resolved by the supervisor where the comparison is made. After the data forms have been keyed, the keying verified, and computer edits completed (see below, Section 9.3.4), the forms will be released for filing in the facility where the examination was performed or to which the mobile team is attached. Some forms will be filed at the Central Laboratory or the data coordinating center. The final disposition of each form is provided in Section 9.2.1.

### 9.3.4 COMPUTER EDITING OF DATA

The keyed data will be edited using specially designed software. Output will be produced which will show items outside acceptable ranges (e.g., a subject who is 80 years old), logically inconsistent (e.g., the subject developed a health condition two years before he was born) and missing. The data entry specialist will be responsible for reviewing this output and determining which items will remain as is and for which data retrieval (requesting information or clarification from the person who completed the form or the study subject himself) will be obtained. Updates will be made when necessary and the data will be continually edited until updating is complete. When correction of a data form is required, a record will be made of the error to document its nature, resolution and the date of resolution.

#### 9.3.4.1 GENERAL EDIT CHECKS

General edit checks will include the following:

- checking for blank fields - if a blank field is not allowed then an error message will be generated
- checking similar data across forms - if discrepancies are found, an error message will be generated

- checking for missing forms
  - checking for logical consistency
- Valid field edits for all variables are specified in detail in the Data Management Manual.

#### 9.3.4.2 EDIT CONSIDERATIONS-SPECIFIC VARIABLES

The following edit checks apply to specific key variables:

- IDs:
  - check for nonnumeric characters
  - check check digit, if there is one
  - check for duplicate IDs
  - check for nonexistent IDs
- Names:
  - check for nonalphabetic characters
  - check for blank field
- Dates-general:
  - check entire field for non-numeric
  - check that month is greater than 0 and less than 13 and that day is greater than 0 and less than 32
  - check that the day of the month is within valid range for the actual month specified (i.e., 1-28, 1-30, 1-31 and 1-29 in leap year)
- Date of birth:
  - compare it against other dates to make sure it precedes them sufficiently
  - check year to make sure it is within study range
- Date of death:
  - compare it against other dates to make sure it follows all activity (alive) dates
  - check year to make sure it precedes the current date and is within the realm of possibility when there are no birth and/or activity years to check
- Postal code:
  - check for nonalphabetic characters
  - check for blank field

#### 9.4 MONITORING PARTICIPANT STATUS

Throughout the course of the study, the status of participants in the study will be monitored using the Study Management System. This system will be used to track the status of individual participants and to prepare reports to monitor recruitment, enrollment, consent, missing information, completed data collection activities and non-response. Staff of the Examination Center is responsible for entry of some of the information into the system. Listed below are the items of information which will be maintained for each participant in the system. A date will be associated with each status.

- recruitment status
- enrollment status
- informed consent status
- non-response status (includes refused and lost-to-followup)
- screening activities completed
- clinic activities completed
- missing data status
- vital status

The system will allow staff of the examination center to view (and print) information on a particular participant and on its own performance. Study management system data will be transmitted to the Data Coordinating Center where additional management reports will be generated.

#### 9.4.1 REPORTS ON STUDY PROGRESS

The Data Coordinating Center and the Epidemiology are responsible for generating reports for the purposes of monitoring study compliance and study progress. These reports are generally produced monthly, or as needed. The following is list of the standard reports to be generated.

- Participant Schedule of Follow-up Visits
- Summary List of Participant Data
- Edit Check Report
- Summary Report of Data Error Types
- Participant Accrual Report
- Participant Status Report
- Ineligible Participant Report
- Status of Dose Estimation

- Building the Cohort Report

#### 9.4.2 REPORTS ON STUDY FINDINGS

The data coordinating center and the Epidemiology group, together with appropriate professional staff will also be responsible for generating reports of study findings. Some standard and some special reports will be required and needs may change as the study progresses. The following standard reports on study findings are expected initially:

- quarterly report on new nodules
- quarterly report on fine needle biopsy
- quarterly report on new thyroid diagnoses
- quarterly report on initial surgeries
- annual report of second and subsequent surgeries

#### 9.5 QUALITY CONTROL

##### 9.5.1 SECURITY

The security of the data in the main file will be protected by passwords to limit access to authorized personnel. Passwords will be periodically changed to maintain security. In addition, the computers will have surge-protectors to guard against power-surges, and data-entry will be backed up systematically. To guard against catastrophic loss of data, e.g., from fire, there will be a duplicate computer file in a different physical location. Finally, all computers and all incoming diskettes will be routinely checked for computer viruses by appropriate programs designed for the purpose.

##### 9.5.2 BACKUPS

Systems will be developed for backing up data at the local examination centers and at the Data Coordinating Center. These procedures are detailed in the Data Management Manual. Also included is information on recovery procedures in case of data loss.

##### 9.5.3 INDIVIDUAL RECORDS

As noted above, each individual data form will be subjected to scanning for completeness, legibility, etc. and double-keyed. Software will be designed for reviewing the logical consistency of the data, the allowable range of numerical entries, and the presence of impossible codes.

##### 9.5.4 STATISTICAL ANALYSIS


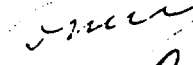

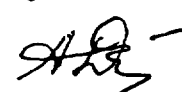
The accumulating data will be statistically analyzed periodically for "drift" or systematic change over time, for consistency among examiners and their equipment, for logical consistency, for patient compliance, and for workload characteristics. In addition, there will be statistical analyses of laboratory results obtained with control samples, and of inter-laboratory results obtained with the same specimens.

This version of Operation Manual is identical as to its content in Russian and English translations.

Agreed:

The American Party

The Ukrainian Party

 V.A. GLIYNYK  
 E.V. EPCHTEIN  
 V. TERESHCHUK  
 A. DEREVYANK

# **R E P O R T**

on implementation of milestones of the 2nd quarter of the  
third year  
of the Joint Ukrainian-American Scientific Project

**" Study of Thyroid Cancer and Other Thyroid Diseases  
in Ukraine Following the Chornobyl Accident"**

(September 1998 - November 1998)

## **Management and administration**

1.9 To prepare continuation of the Agreement according to the Project.

Documents have been prepared, concerning continuation - beginning from July 1, 1998 for 12 months - of Project Partner Agreement between the Science and Technology Center of Ukraine, the Institute of Endocrinology and Metabolism of the Academy of Medical Sciences of Ukraine, and the National Cancer Institute of the U.S.A. on implementation of milestones of the 2nd quarter of the 3rd Year of the Ukr.-Am.

Project "Scientific Protocol for the Study of Thyroid Cancer and Other Thyroid Diseases in Ukraine Following the Chornobyl Accident"

1.10 To apply to the State Administration of the Kozelets raion of Chernihiv oblast in order of providing a coach for transporting cohort members for the period of screening.

A letter from Dr. A. Serdyuk, Minister of Public Health of Ukraine, to the Head of the State Administration of Chernihiv oblast has been prepared, with a request to provide a coach for transporting cohort members in order of screening to the Clinic of the Institute of Endocrinology and Metabolism, Acad. Med. Sci. Ukraine, for the period of screening performance in Kozelets, Chernihiv, and Ripky raions of Chernihiv oblast. The Administration of Chernihiv oblast has taken a decision to provide a coach.

#### 1.11 To ensure printing of Examination Forms in a printing-house.

All screening Forms, intended for 5.000 cohort members, have been printed in printing-house.

#### 1.12 To organize and hold a regular joint meeting devoted to Project implementation (with participation of the Ministry of Public Health of Ukraine, Management and Co-executors of the Project).

A joint meeting of Ukrainian and American participants in the Project, together with representatives of the Ministry of Public Health of Ukraine, has been organized and held on October 28, 1998, devoted to progress in Project implementation, priority areas of further work.

#### 1.13 To work with custom clearance documentation.

Documentation for customs clearance has been prepared for shipments which have been received within the reported period (list of shipments enclosed).

### 2. The establishment of the cohort

2.7 To complete input of data from paper carriers, obtained as a result of manual search in Chernihiv and Kozelets raions of Chernihiv oblast.

Computer entry of data obtained as a result of manual search in Chernihiv oblast has been completed. For the Kozelets raion of Chernigiv oblast data have been entered on 1796 persons (out of 2089 members of intensive cohort), what makes 86%. The status of the other 293 cohort members is unknown. Out of them 1337 persons are currently living in Kozelets raion (64%). For the Chernihiv raion of Chernihiv oblast data have been entered on 2409 persons (out of 2858 members of intensive cohort), what makes 84%. The status of the other 449 cohort members is unknown. Out of them 1905 persons are currently living in Chernihiv raion (66%). In all, data on 4205 persons have been entered (Kozelets and Chernihiv raions), 3242 of which have not changed their place of residence, what makes 65%.

The status of cohort members found as a result of manual search, is distributed as follows:

Raions	Chernihiv		Kozelets		Total
	N	%	N	%	N
Found	1905	66,7	1337	64,0	3242
Not found(status not defined)	449	15,7	293	14,0	742
Moved to another oblast of Ukraine	25	0,9	17	0,8	42
Moved abroad	22	0,8	13	0,6	35
Moved in unknown direction	253	8,9	88	4,2	341
Provisionally absent in the settlement	33	1,2	50	2,4	83

Died	14	0,5	8	0,4	22
Duplicated	156	5,5	15	0,7	171
Provisionally living in the settlement	1	0,0	268	12,8	269
Total	2858	100,0	2089	100,0	4947

An analysis of the data entered has shown that as a result of manual search, in specifying the date of birth 6 persons born before 1968 have been revealed. These persons have a year of birth which does not meet the criteria of cohort formation.

2.9. To input data from paper carriers, obtained as a result of manual search in Narodychi raion of Zhytomyr oblast.

The Data Coordinating Center has drawn up a program for obtaining and printing of tables which reflect the dynamics of patients' invitation (Appendix 1). The patients are sorted according to the settlements and in alphabetical order.

These tables have been printed according to the dynamics of patients' invitation for the Narodychi raion of Zhytomyr oblast for each settlement. The tables include all the members of the 20.000-cohort who were living in 1986 in Narodychi raion (a total of 4279 persons).

On the request of the American colleagues, the Data Coordinating Center has drawn up a program for calculation of the distribution of the 75.000-cohort's members according to the doses, sex and year of birth. The distribution presents the following aspect:

## Dose "A" (&lt;30cGy)

Sex	• male	• Female	Not defined	Total
Year of birth				
1968-1971	2562	3214	1212	6988
1972-1976	7630	8320	3192	19142
1977-1981	5094	5522	2411	13027
1982-1986	2600	2734	1621	6955
Not defined	116	164	88	368
Total	18002	19954	8524	46480

## Dose "B" (30cGy&lt;B&lt;100cGy)

Sex	• male	• Female	Not defined	Total
Year of birth				
1968-1971	905	689	204	1798
1972-1976	2571	2276	683	5530
1977-1981	2566	2304	773	5643
1982-1986	2181	2301	873	5355
Not defined	180	181	52	413
Total	8403	7751	2585	18739

## Dose "C" (C&gt;100cGy)



Sex	• Male	• FeMale	Not defined	Total
Year of birth				
1968-1971	402	245	39	686
1972-1976	1209	882	109	2200
1977-1981	1229	1114	163	2506
1982-1986	1933	1840	356	4129
Not defined	202	244	103	549
Total	4975	4325	770	10070

### 3. Invite the subjects for endocrinologic screening

3.1 To continue invitations by the telephone of the cohort members currently living in Kyiv which were resettled from Chornobyl and Prypyat.

Invitation by the telephone of cohort members currently living in Kyiv and were resettled from Chornobyl and Kyiv continued.

*Number and distribution of patients left unexamined in Kyiv.*

Date	People left anexamined	Number of people examined in Kyiv	Missing <sup>1</sup> 	Wrong <sup>1</sup> 	Refuses to come for examination after second invitation	Telephone contacts: total	Were examined in 05.1997
30.12	119	294	41	30	48	650	12
%	28,8	71,2	9	7,2	11,6		2,9
Total 413 persons							

Were send letters of invitation to the cohort members left unexamined – 119.

41- to the patients with unknown telephone number, 30 – to the patients with wrong telephone numbers, 48 – to those who refused to participate while contacted by the telephone.

By 30.11.98 22 cards with reply returned.

19 respondents agreed to participate in the examination and were given the date of appointment .

2 persons refused to participate because they are under medical surveillance in the other medical facility.

1 cohort member is currently living in Brussels. In 1996 she was

operated on because of thyroid cancer and underwent total thyroidectomy in Brussels.

3.2 To obtain consent to take part in screening from cohort members who reside in Ovruch raion, Zhitomir oblast.

Consent to take part in screening was obtained by local medical staff. To the medical staff of Ovruch raion was send a form to clarify reasons of not coming of some subjects to the examination and to assess the possibility of their recruitment into the study. The form and instruction to fill in is in App.1.

Invitation of subjects of Narodichi raion started. Epidemiologists-members of mobile team were receiving the information about the patients who didn't come for the screening from local medical staff during screening and were filling in form 'Dynamics of invitation of patients for the screening' (App. 1)

3.3 To publish in the Ovruch local newspaper an article clearing up the purposes of the screening of the population of Ivankiv raion in the framework of the Ukr.-Am. Project.

In the Ovruch local newspaper was published an article about goals of the Ukr.-Am project.

3.4 To give a broadcast talk on the local radio of Ovruch raion in order to inform the population about purposes and tasks of the Ukr.-Am.

## Thyroid Project.

Was given broadcast talk on the Ovruch local radio with the information about purposes and tasks of the Ukr. - Am. Project.

On the basis of the information received on consent to take part in the screening, to make a schedule of screening of the population of the Ovruch raion, and Kyiv which was resettled from Chornobyl and Prypyat.

Schedule of the examination of the population of the Ovruch raion was made by local medical staff based on their personal contacts.

Schedule of examination of the subjects, currently living in Kyiv, was made by members of epidemiology group based on the telephone contacts and correspondence.

## Endocrinologic examination of the subjects

4.3 To continue screening by stationary team of cohort members who have been evacuated from Chornobyl and Prypyat to Kyiv.

4.5 To continue screening by mobile teams of cohort members who are residing in Ovruch raion.

Place of screening: Zhytomyr oblast, Ovruch raion: village Khluplyany, village Sloboda, village Pershotravneve, city of Ovruch, village Bondary, village N. Velednychy, village Pokaliv, village V. Chernihivka, village Ignatpil.

Clinic of the Institute of Endocrinology and Metabolism (persons evacuated from the city of Prypyat)

Number of persons examined: 906

Diffuse goiter, degree 1: 226 persons

Diffuse goiter, degree 2: 55 persons

Nodular goiter, degree 1: 3 persons

Nodular goiter, degree 2: 9 persons

Mixed goiter, degree 1: 1 person

Mixed goiter, degree 2: 4 persons

Autoimmune thyroiditis: 1 person

Postoperative hypothyroidism: 1 person

Mixed goiter, degree 2: 1 person - examination and treatment have been performed at the Institute of Endocrinology and Metabolism.

Papillary thyroid carcinoma: 1 person (clinical treatment until November 24, 1998).

### **Operation of the Central Laboratory**

5.2 To perform all the laboratory tests in the process of screening.

The following examinations have been performed by the Central Laboratory:

a) blood hormone level:

Thyrotropin: 417 persons

Thyroglobulin: 228 persons

Anti-TPO: 418 persons

b)  $\text{Ca}^{++}$  level and pH in blood: 960 patients.

FNAB of thyroid nodules has been performed in 10 patients.

Thyroid cancer has been revealed in one person.

## **6. Operation of Data Coordinating Center**

### **6.1. To complete installation of software and hardware.**

A second network adapter has been installed on Windows NT 4.0 server. Two subnets of C class have been determined (the first subnet for the server and 5 work stations, the second one for the server, printer and old computers). A 10Mb/s repeater (HUB) has been connected to the second subnet. A printer Minolta PagePro 12 has been connected to the 10Mb/s segment of network. IP addresses in the framework of C class network have been determined for all work stations and printer. In the operation system Windows NT 4.0 static tables of routing have been described so that the computers of both subnets might have access to each another and to the printer. Utility Minolta TCP/IP networking has been installed and adjusted on work stations. At present, the printer is operating in real network regimen.

Operation system Windows 95 and necessary program packets for 3 working stations Deskpro 4000S (P2200; 32 PAM; 3,1Gb;15") have been installed; one computer has been installed in Project Office; HP Laser Jet 5L printer has been connected to it, and necessary software has been installed.

A device for recording USI images on magneto-optical discs has been connected and adjusted to USI-apparatuses TOSBEE & HITACHI. Staff (physicians and USI operators) has been trained for operation with the image recording device Camtronics.

One of the old computers has been provided to the translator. Because of its insufficient power, an operation system Window 3.11 and version 6.0 MS Word have been installed on it.

6.2. To complete study and management of the database InterBase server.

DBMS InterBase has been installed on the server. The language of structured requests SQL has been studied, as well as InterBase Interactive SQL. The server has been configurated for access of 4 clients, rights to access to DataBase have been established.

6.3. Recompilation of available databases into InterBase format.

DataBase has been translated into InterBase format. To date, the base is available in two versions:

- an old version in PARADOX format;
- a new version in InterBase format.

So far, the old version of database is used, because, for using new databases in InterBase format, it is necessary to transfer all existing programs on SQL platform. This requires additional work and time for programming.

6.13. To work out a complex of programs for the Pathology Group.

Necessary software has been installed on one of the old computers, and this computer has been provided to the Pathomorphology Department. At present, the computer is operating separately from the network. This is due to technical difficulties of connecting a 10 Mb/s network adapter to the available 100 Mb/s network.

Due to the necessity of working out programs for Screening Forms, realization of Pathology Form has been postponed to later terms. This milestone will be implemented as soon as programs for input of Screening Forms will be developed.

6.14. To work out a database and computer form of input of data for the Locator Form.

A database structure for storage and input of data from paper version of Locator Forms has been developed. The base's structure presents the following aspect:

NAME OF FIELDS	TYPE	COMMENTS
ID	A(8)*	Identification number
Date	D *	Date of completion of the Form
KOD_ZAP	A(3)	Code of the operator having completed the Forms
KOD_INPUT	A(3)	Code of the operator having input data in computer
MS_OBSLED	S	Place of examination: 0- Polyclinic of IE&M 1- Mobile team
NEXT_DATE	D	Date of presumed leaving

NEXT_NP	A(8)	Code of presumed settlement after leaving
NEXT_COMMENT	Memo	Comments
NEXT_ADRESS	A(30)	Address of presumed place of residence. Includes: Street, Building, and Apartment.
FIO_86	A(15)	Surname in 1986
OTHER_NP	A(8)	Other place of residence. Includes: code of Oblast, Raion, Village Council, Settlement
OTHER_ADRESS	A(30)	Other place of residence. Includes: Street, Building, and Apartment.
WORK_PLACE	Memo	Patient's place of work/studies
PROFESSION	Memo	Profession (position)
WORK_NP	S	Office address. Includes: code of Oblast, Raion, Village Council, Settlement
WORK_ADRESS	A(30)	Office address. Includes: Street, Building, and Apartment
RAY_POL_N	S	Number of patient's raion polyclinic
RAY_POL_TIP	S	Polyclinic's type: 0- for children 1- for adults
RAY_POL_NP	S	Polyclinic's address. Includes: code of Oblast, Raion, Village Council, Settlement
RAY_POL_ADRESS	A(30)	Polyclinic's address. Includes: Street, Building, and Apartment
RAY_POL_TEL	A(12)	Polyclinic's telephone number

DB structure "Patient's relations" RODSTVO.DB

- contains information on patient's relations. Used in "Locator Form". (\* - key fields)

NAME OF FIELDS	TYPE	COMMENTS
ID	A(8)*	Identification number
Data	D *	Date of completion of the Form
RODSTVO	S *	Degree of relationship: 0-Mother 1-Father 2-Brother/Sister 3-Husband/Wife 4-Other
FAM	A(15)	Surname
IM	A(10)	First name
OT	A(15)	Patronymic
TEL	A(12)	Telephone number of patient's relation
NP	S	Relation's address. Include: code of Oblast, Raion, Village Council, Settlement
ADRESS	A(30)	Relation's address. Includes: Street, Building, and Apartment
GENERAL_NOTES	Memo	General notes

DB structure "Patients' telephones" TELEFON.DB

- contains patients' telephone numbers.

(\* - key fields)

NAME OF FIELDS	TYPE	COMMENTS
ID	A(8) *	Identification number -
TIP	S *	Telephone type: 0- Home 1- Office 2- School 3- Other
TEL	A(12)	Telephone number of patient's relation
GENERAL_NOTES	Memo	General notes

A program for input of data from the paper version of the Locator Form into the database of the Project has been created. This program maximally controls the completeness of all necessary fields of Form and performs quality control (it does not allow input of incorrect data, settlements).

A database's structure for storage and information on the dynamics of invitation and status of cohort members has also been developed:

NAME OF FIELDS	TYPE	COMMENTS
ID	A(8)*	ID
DateFirstCont	D	Date of first contact
Result	S	Result (examination, etc.)
REFIUSE	S	Cause of refusal to participate in screening
DateNextCont	D	Date of next contact
ResultNext	S	Result of next contact
KODTEAM	S	Code of the team having performed examination
NOTE	M	Note

as well as a DB of schedule and composition of mobile teams.

DB structure "Schedule and composition of mobile teams"

MOBTEAMS.DB

(\* - key fields)

NAME OF FIELDS	TYPE	COMMENTS
KodTeam	S*	Team's code (1 - fixed team)
DateOut	D	Date of departure
DateIn	D	Date of return
HEADS	S	Team head's code
NP_EXAM	A(8)	Settlement where examination has been performed
EXAMENED	S	Number of subjects examined

DB structure "Mobile teams' composition" SUBTEAMS.DB (\* - key fields)

NAME OF FIELDS	TYPE	COMMENTS
KodTeam	S*	Team's code
MEMBERKOD	A(3)	Team member's code

The Data Coordinating Center has begun input of screening data (Locator Forms) in the database of the Project.

In addition, DCC has prepared a database for the persons who are residing in Kyiv but do not have a telephone, or give their verbal consent but do not come to examinations (119 potential cohort members).

A program has been developed for printing post-cards and printing addresses on envelopes. On the base of the above-mentioned base, 119 invitations, post-cards and envelopes for potential cohort members have been printed.

### **Pathology support for diagnosis of various forms of thyroid pathology.**

7.1. To continue collecting and pathological examination of morphologic material from all patients born in 1968 and later from cohort oblasts and having been operated at the Institute of Endocrinology for different thyroid diagnoses. Pathomorphologic analysis of collected material.

Collection of biopsy material has been continued in the form of paraffin blocks and histological preparations from patients born in 1968

and later, who reside in Kyiv oblast (including city of Kyiv), Chernihiv, Zhytomyr oblasts and have been operated at the Clinic of the Institute of Endocrinology during the reported period for different types of thyroid pathology. For the period September-November 1998, material from 31 cases of surgical thyroid pathology has been collected. They include 9 cases of thyroid carcinoma (one case from Kyiv oblast, 2 from Chernihiv oblast, 2 from Zhytomyr oblast, and 4 from the city of Kyiv); 5 cases of follicular adenoma (3 from Chernihiv oblast, one from Zhytomyr oblast and one from the city of Kyiv); 11 cases of nodular goiter (5 from Kyiv oblast, one from Chernihiv oblast, 2 from Zhytomyr oblast, and 3 from the city of Kyiv); 2 cases of multinodular goiter (one from Kyiv oblast and one from the city of Kyiv); and 4 cases of diffuse toxic goiter (one from Kyiv oblast, one from Zhytomyr oblast, and 2 from the city of Kyiv).

With diagnostic purpose, 250 blocks have been embedded in paraffin, and more than 500 histological preparations have been studied at light microscope.

8 from 9 (89 %) of the studied cases of thyroid cancer represented a papillary carcinoma. 3 tumors of this type were removed in children aged 12-13 years (at the time of the accident these children were aged from 5 months to 1 year and 5 months), and 5 tumors were removed in young adult patients aged 22 to 29 years.

As to their histological structure, the papillary carcinoma in children has been verified in one case as an oxyphilic-cell follicular variant, in one case it was a mixed papillary-follicular structure, and in one case a typical papillary structure, oxyphilic-cell variant. It should be noted that in 2 from 3 cases in children, metastases in regional lymph nodes were reported.

In adult patients 2 from 5 cases of papillary carcinoma had a typical papillary structure, in one case a solid structure, in one case a mixed papillary-follicular structure, and in one case a diffuse-sclerosing variant of papillary carcinoma was noted. In 3 cases there were signs of a concomitant chronic thyroiditis. Metastases in regional lymph nodes in adult patients were reported in 4 cases.

A minimally invasive follicular adenoma has been verified in one patient (female) aged 25 years from the city of Kyiv.

Two follicular adenomas with microfollicular and solid structure were reported in children aged 13-14 years; two follicular adenomas of heterogenous structure with areas of papillary hyperplasia and oxyphilic-cell proliferation, and with microfollicular-solid structure in adolescents aged 15 and 17 years, and one normofollicular adenoma in an adult patient (female) aged 28 years.

Nodular solitary goiters have been established in 3 children aged 13-14 years and in one child aged 11 years (a girl from Kyiv oblast born in 1986, i.e. "in utero" at the time of the accident); in one adolescent aged 16 years, and in 6 adult patients aged 20 to 28 years. The goiters had a dominant macro-normofollicular structure with presence of cystic cavities. Only in 3 cases there were no signs of cystic transformation.

A multinodular goiter of heterogeneous histological structure with presence of cystic cavities has been verified in one boy aged 13 years and in one adult patient (female) aged 29 years.

*Diffuse toxic goiter* was present only in young adult patients aged 20 to 28 years. In all cases there were signs of alveolar papillary hyperplasia,

sclerotic changes, and in 2 cases signs of a concomitant chronic thyroiditis were noted.

7.2. Preparation of additional histological specimens for the morphologic data bank of the Ukr.-Am. Project from patients including in the cohort.

A detailed information on the above cases, which included patient's passport data, exact date of birth, place of residence during the accident and to date, has been provided to the Dosimetry Department of the Scientific Center of Radiation Medicine and to DCC in order to identify persons who had direct measurements of thyroid activity and were included in the cohort. It has been established that among the subjects who have been operated within the reported period, 2 patients belonged to the cohort under study. One of them, a male born in 1972 (group "C" of the 20000-cohort), from the Ovruch raion of Zhytomyr oblast has been operated on for an encapsulated papillary carcinoma of solid structure, and the second patient, a female born in 1976, also from the Ovruch raion of Zhytomyr oblast (group "A" of the 75000-cohort) has been operated on for a nodular solitary goiter of heterogeneous histological structure. Additional histological preparations have been prepared from the paraffin blocks of the above cases for the morphologic data bank of the Ukr.-Am. Project.

Thus, in the morphologic data bank of the Ukr.-Am. Project, among the cases identified in the cohort, at present moment 23 cases of thyroid carcinoma and 9 cases of benign pathology (2 follicular adenomas, 3

multinodular goiters, 3 nodular solitary goiters, and one diffuse toxic goiter) are established.

Together with DCC, an additional analysis of the above cases has been made as regards the distribution of patients in the 20000-cohort, 75000-cohort, and general 100000-cohort.

So, among 23 cases of thyroid carcinoma, 10 (43.5 %) belong to the 20000-cohort (group "C"), 8 cases (34.8 %) to the 75000-cohort (3 cases in group "B" and 5 cases in group "A"), and 5 cases (21.7 %) belong to the general 100000-cohort (one case in group "C", one case in group "B", and 3 cases in group "A").

Among 9 cases of benign thyroid pathology, 5 cases (55.6 %) belong to the 75000-cohort (one case in group "B" and 4 cases in group "A"), and 4 cases (44.4 %) belong to the general 100000-cohort (all the cases in group "B").

7.3. To ensure intraoperational diagnosis, histological processing and pathomorphologic analysis of specimens received from patients selected for surgery after screening. Preparation of additional histological specimens for the morphologic data bank of the Ukr.-Am. Project.

Screening examinations performed to date allowed to identify only one patient for surgery, a girl born in 1984 from the Ovruch raion of Zhytomyr oblast, with presence of a thyroid nodule, and, according to FNAB results, a thyroid carcinoma was suspected in this case. This girl has been hospitalized at the Department of Children's Endocrine Pathology of the Institute, and the operation was scheduled for December

1, 1998. The report on the morphologic structure of the tumor will be presented in the next quarter.

7.4 To fill in the Pathology Forms for the patients with revealed cases of thyroid pathology, included in the cohort under study. To set these data into the computer and provide them to DCC (after receipt of computers).

The Pathology Forms for the above cases have been filled in on paper. The Laboratory has been provided with a computer which was formerly (before installation of new modern equipment) used in DCC. After the DCC staff will have developed the appropriate programs, the Forms will be completed on computer, but so far data transfer to DCC is impossible, because there are problems with network communication and incompatibility of diskette size between the computer provided to the Laboratory and new computers installed in DCC.

## DOSIMETRY SUPPORT OF THE "UKRAINIAN-AMERICAN SCIENTIFIC PROJECT ON THE STUDY OF CANCER AND OTHER THYROID DISEASES IN UKRAINE AS A CONSEQUENCE OF THE CHORNOBYL ACCIDENT"

8.7. to support the questionnaire db. questioning, input and computer support of questionnaires' information. dose reconstruction on the basis of questionnaire data.

In the second quarter of the 3rd year of Project implementation, 943 persons have been questioned. Questioning was performed by interviewers from mobile teams which were operating in settlements of the Ovruch's'kyi raion of Zhytomyrs'ka oblast (773 persons questioned), as well as at the Institute of Endocrinology and Metabolism (170 persons questioned). Among these 943 persons, 716 were subjects who were aged under 10 years at the time of the accident.

The distribution of the questionnaires collected in the 2nd quarter, according to the regions of location of the persons questioned during the accident, is shown in Table 8.7.1. The total number of questionnaires collected in the process of Project implementation, and their distribution is given in Table 8.7.2.

Table 8.7.1. - Distribution of questionnaires collected in the 2nd quarter of the 3rd year of Project implementation, according to the regions of location during the Chornobyl accident

Location of the persons during the Chornobyl accident	Number of questionnaires collected	Including: number of questionnaires of persons who were aged under 10 years at the accident
Ovruch's'kyi raion, Zhytomyrs'ka oblast	773	585
City of Prypyat'	153	121
Chornobyl's'kyi raion, Kyivs'ka oblast	15	8
Ivankiv's'kyi raion, Kyivs'ka oblast	1	1

Polis'skyi raion, Kyivs'ka oblast	1	1
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Table 8.7.2. - Total number of questionnaires collected in the process of Project implementation and their distribution according to the regions of location during the Chornobyl accident

Location of the persons during the Chornobyl accident		Number of questionnaires collected
Kyivs'ka oblast	City of Prypyat'	260
	Chornobyls'kyi raion	15
	Ivankivs'kyi raion	183
	Polis'skyi raion	1
Cherhiivs'ka oblast	Kozelets'kyi raion	105
Zhytomyrs'ka oblast	Ovruchs'kyi raion	773
Total		1337

#### 8.15. VERIFICATION OF THYROID MEASUREMENTS. DEVELOPMENT OF A TECHNIQUE FOR RETROSPECTIVE ASSESSMENT OF "DEVICE"-SPECIFIC ("LIST"-SPECIFIC WHERE IT IS POSSIBLE) CALIBRATION FACTORS FOR DEVICES WITH FAILED DATA OF CALIBRATION.

After having analyzed all the data for devices' calibration factors available in Lists, we have classified and divided them into three calibration classes.

1. The List contains all the data on the date of preparation of source, its activity, and the results of measurements of the control source are available; the calibration factor may be calculated.
2. The List contains the calibration factor written down by the dosimetrist, but it is impossible to verify it because of lack of necessary calibration data. Such factors are found for spectrometric devices which have been used for measurements at early stages of thyrodosimetric monitoring. We think that in these cases calibration was performed before going to the place of measurements.
3. The Lists pertaining to SRP-68-01 type devices do not include calibration data. One uses as calibration factor for such Lists a universal factor equal to  $6.25 \cdot 10^{-3} \mu\text{Ci} \times \text{R}^{-1} \times \text{h}$ .

The Table 8.15.1. shows the distribution of all available Lists with measurements

according to the type of device (spectrometric, non spectrometric) and calibration class.

Table 8.15.1. - Distribution of calibration factors according to the type of device and calibration class

Device's type	Calibration class according to calibration factor (CF)	Number of Lists	% of measurements
<b>Spectrometer</b>	Class 1. CF can be verified	245	23%
	Class 2. Verification of CF is impossible	65	13%
<b>Counter (SRP)</b>	Class 1. CF can be verified	194	17%
	Class 3. Universal for all device average CF	573	47%

\* 10 Lists performed using non spectrometric devices of DP-6A and PRL types (0.15% of measurements) have been excluded being considered as Lists containing measurements of uncertain quality.

We think that one of the reasons of such an uncertainty of dose estimates obtained for measurements made with SRP-68-01 devices is due to the following fact. Even after a retrospective restoration of the results of calibration of SRP-68-01 devices, calibration data are still missing for 573 Lists (74 % of measurements made with devices of this type. or 47 % of all measurements). One uses for these a universal calibration factor for all SRP-68-01 devices equal to  $6.25 \cdot 10^{-3} \mu\text{Ci h } \mu\text{R}^{-1}$ .

Formerly (see the report for the 4th quarter of the 2nd year of Project implementation, milestone 8.14.2.2), we noted that the counting efficiency for different SRP-68-01 devices significantly differed, and application of a universal calibration factor for all devices is not advisable. We see a solution of this problem in dividing all the devices with missing calibration data into groups, with subsequent use, within each group, of its own average calibration factor which is specific for this group.

In order to ascertain the correctness of division of all devices with missing calibration data on groups, we have analysed the routs of displacements of dosimetric teams, concrete team members and certain devices on the areas of measurements. We have also analysed the cases of use of each device in several teams; the cases of

operation of each dosimetrist with different devices; the cases of operation of each dosimetrist when included in several teams. One used for this analysis information on dosimetric team's code, dosimetrist's personal signature and device's serial number available in primary records and set, in the process of implementation of previous stages of work, into the DB MEASUR (report for the 4th quarter of the 2nd year of Project, milestone 8.14.1.1).

The thyroid monitoring measurements of children who had been during the accident in 8 regions of Ukraine established by the Protocol of cohort screening and in the city of Prypyat, have been performed on the territories of the city of Kyiv and 13 regions of Ukraine: Zhytomyrs'ka, Kyivs'ka, Chernihivs'ka, Rivnens'ka, Vinnyts'ka, Khmelnyts'ka, Ternopil's'ka, Lvivs'ka, Sums'ka, Odes'ka, Donetsk, Zaporizhs'ka oblasts, and Crimea (enumeration of dosimetric teams is given in Table 8.14.1 of the report for the 4th quarter of the 2nd year of Project). The codes of teams which have operated in each oblast, consisted of the first letter (or two first letters) of the name of the oblast and of team's number.

It has been established that:

- (a) The same device might have moved from one team to another, but only within the territory of one oblast. The displacement of a same device in different raions within one oblast was also a usual occurrence. The Table 8.15.2 gathers all the cases where the same device was used by several dosimetric teams; as seen from the Table, each of devices was used only in teams of one oblast. Only one device (UR 1-3 Serial # 912001) is an exception, having been used for measurements in three oblasts.

TABLE 8.15.2-LLIST OF DEVICES WHICH HAVE BEEN USED IN SEVERAL DOSIMETRIC TEAMS

Device	Device's serial number	Dosimetric teams having used the device	Oblasts where dosimetric teams were operating
GTRM-01ts	32	ch-1, ch-14	Chernihivs'ka
NK-150	71077	ch-10, ch-16, ch-3	Chernihivs'ka
NK-350	81031	ch-11, ch-12	Chernihivs'ka

UR 1-3	912001	k, lv-1, ch-3	Kyivs'ka, Chernihivs'ka, Lvivs'ka
SRP-68-01	1727	kr-1, kr-2, kr-9	Crimea
SRP-68-01	2113	o-1, o-17	Odes'ka
SRP-68-01	863	o-1, o-18	Odes'ka
SRP-68-01	1086	o-1, o-2	Odes'ka
SRP-68-01	2085	o-10, o-4	Odes'ka
SRP-68-01	1670	o-12, o-2, o-9	Odes'ka
SRP-68-01	125	zh-1, zh-2, zh-3	Zhytomyrs'ka
SRP-68-01	149	zh-1, zh-2, zh-3	Zhytomyrs'ka
SRP-68-01	268	zh-1, zh-2, zh-3	Zhytomyrs'ka
SRP-68-01	914	zh-3, zh-4	Zhytomyrs'ka
SRP-68-01	1385	zh-4, zh-5	Zhytomyrs'ka
SRP-68-01	268	zh-5, zh-8	Zhytomyrs'ka
SRP-68-01	854	zh-7, zh-8	Zhytomyrs'ka

- (a) The dosimetrists also moved from one team to another (one dosimetrist might have worked in four different teams) and from one raion to another, but only within one oblast. Only one case is an exception to the rule, when a dosimetrist made measurements on the territory of two oblasts. This dosimetrist was operating with the above-mentioned device UR- 1-3, Serial # 912001.

An analysis of displacements of dosimetric teams, concrete dosimetrists and devices on the territories of measurements allowed to draw the following conclusion. In spite of the fact that the direction of measurements of thyroid activity on the Ukrainian territory was a centralized one, in each oblast where measurements were performed a local dosimetric group and kit of measuring devices were formed. All the above-mentioned allows to consider kits of devices and features of measurements which are specific for concrete oblasts of measurements.

THE FIG. 8.15.1 GIVES LIST-SPECIFIC CALIBRATION FACTORS ( $CF$ ) FOR SRP-68-01 DEVICES, WHICH ARE CLASSIFIED ACCORDING TO THE OBLASTS WHERE MEASUREMENTS WERE PERFORMED. AS APPEARED FROM THIS FIGURE, THE FACTORS IN DIFFERENT OBLASTS ARE ON DIFFERENT LEVELS. THE AVERAGE  $CF$  FOR OBLASTS SIGNIFICANTLY DIFFER FROM THE AVERAGE FACTOR EQUAL TO  $6.25 \cdot 10^{-3} \mu\text{Ci H } \mu\text{R}^{-1}$  WHICH WAS ADOPTED FOR CALCULATIONS. THE VALUES OF AVERAGE  $CF$  FOR OBLASTS WERE EQUAL:

FOR ZHYTOMYRS'KA OBLAST –  $7.34 \mu\text{Ci H } \mu\text{R}^{-1}$ , VINNYTS'KA OBLAST –  $12.49 \mu\text{Ci H } \mu\text{R}^{-1}$ , CRIMEA –  $2.38 \mu\text{Ci H } \mu\text{R}^{-1}$ , LVIVS'KA OBLAST –  $1.39 \mu\text{Ci H } \mu\text{R}^{-1}$ , ODES'KA OBLAST –  $3.79 \mu\text{Ci H } \mu\text{R}^{-1}$ , RIVNENS'KA OBLAST –  $3.13 \mu\text{Ci H } \mu\text{R}^{-1}$ .

In our opinion, this is due to the fact that in each oblast a group of dosimetrists was formed for the teams of this oblast. Therefore, in different oblasts a different geometry of measurements might have been used, for instance: the prominent part of the collimators might have been different, and, therefore, the efficiency of registration was also different.

As a result of the analysis, it has been decided that for SRP-68-01 devices with missing calibration data, oblast-specific calibration factors may be used instead of a universal calibration factor for all devices.

In order to verify the correctness of this decision, we have analysed 1550 results of double measurements, when the thyroid was measured in the same person simultaneously with two devices: a spectrometric one and SRP-68-01. One may see on Fig. 8.15.2. as an example, the results of assessment of average age-dependent doses in a couple of measurements made with spectrometric devices NK-350 #82014 and SRP-68-01 #1757 (inhabitants of Vyshgorod and Makarov raions of Kyivs'ka oblast evacuated to the Crimea,

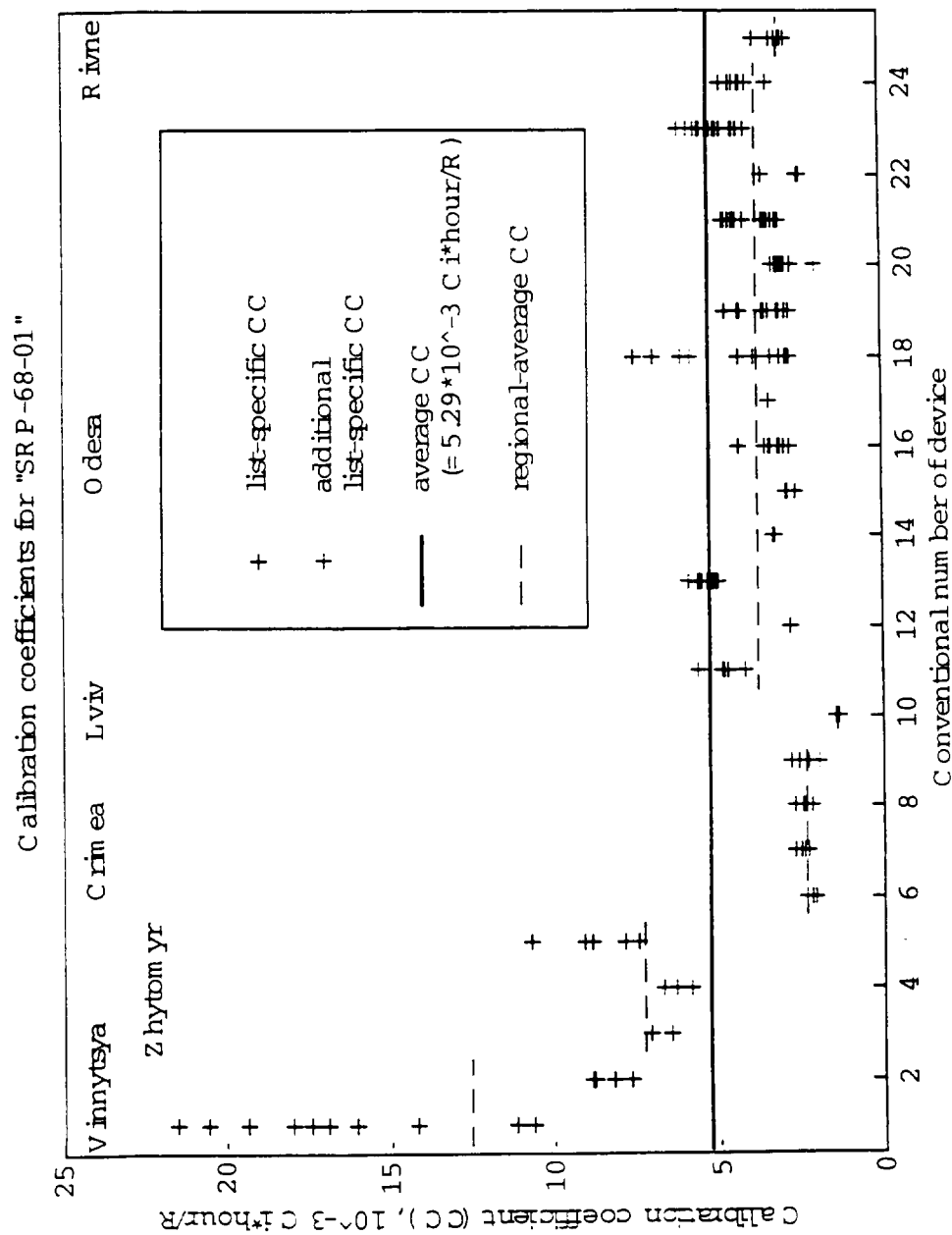


Fig. 8.5.1. Calibration factors of SRP-68-01 devices classified according to the oblasts of measurements.

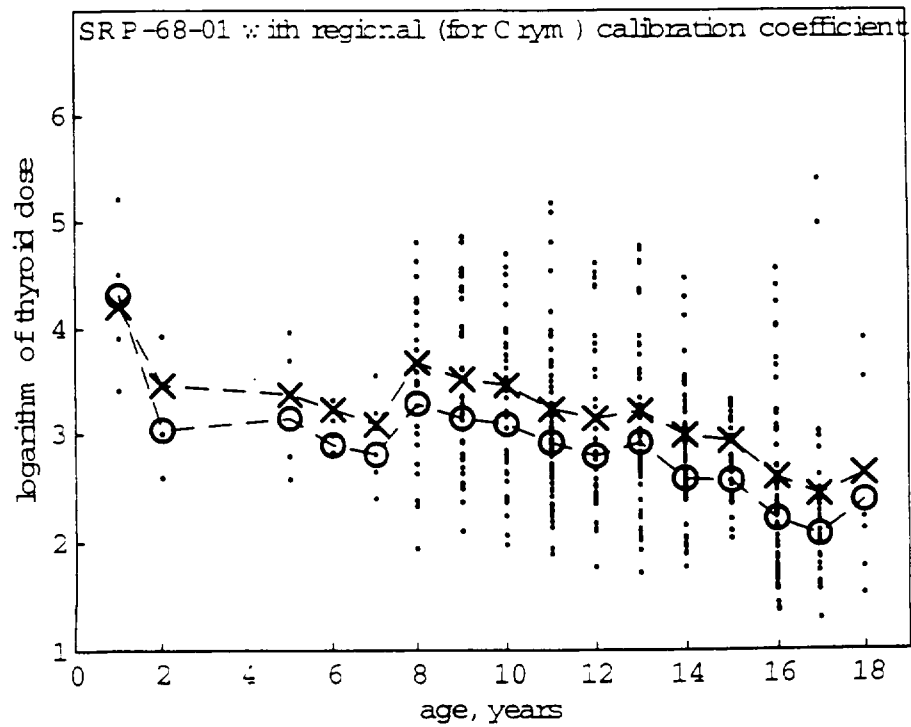
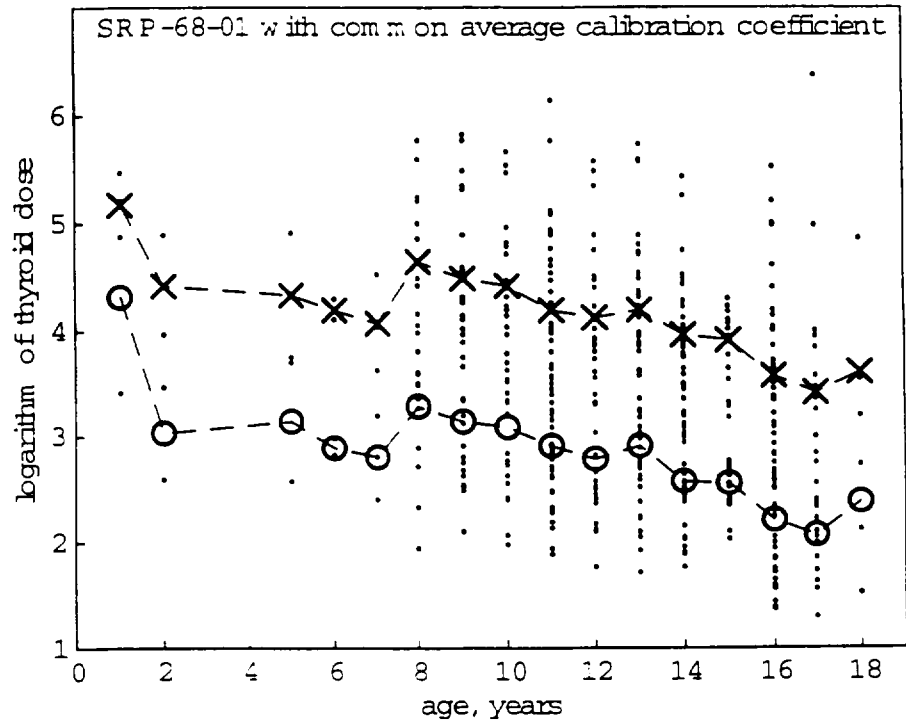


Fig. 8.15.2. Age-dependent average doses calculated according to the data of spectrometric and non

spectrometric measurements made simultaneously in the same persons (circles: NK-350, crosses: SRP-68-01).

258 couple of measurements). Upper part of the figure: there was no  $CF$  for SRP-68-01 #1757, and one used the old average factor for all SRP equal to  $6.25 \cdot 10^{-3}$ . One may see that the doses calculated according to SRP-68-01 data are higher for all ages. It has not been additionally found results of calibration for the device with this serial number, and on the lower figure an oblast-specific average  $CF=2.38 \cdot 10^{-3} \mu\text{Ci h } \mu\text{R}^{-1}$  for Crimea has been used for it. As appeared, it significantly improves the correspondence of spectro- and non spectrometric data.

Unfortunately, oblast-specific calibration factors for SRP-68-01 devices may have been calculated only for 6 from 13 oblasts where measurements had been performed. It was also impossible to calculate it for the devices, which had been used in the city of Kyiv.

Therefore, we tried to develop a technique for restoration, where it is possible, of the device-specific calibration factor for a device with a concrete serial number, if it had no calibration data. The technique uses the procedure of comparative analysis for the doses calculated according to the data of measurements with different devices on samples of the same type (as concerns location at the time of the accident and age), of subjects measured.

The procedure of comparative analysis includes the following steps:

1. Forming of samples of results of measurements of doses performed with devices with available results of calibration and calculated  $CF$  (**high quality**) and a device with a concrete number and unknown or tested  $CF$  (**low quality**). The samples are formed provided that measurements are to be performed in the same Local Council ( $LC$ ), in the same age group, in number of at least 12 measurements of each quality.
2. For each Local Council ( $LC$ ) and each age group ( $age$ ) the correction factor  $K$  is calculated:

$$K(age, LC) = \frac{D_{low}(age, LC)}{D_{high}(age, LC)}$$

where  $D_{low}(age, LC)$  is the average dose of low quality in the  $LC$  in question and age group in question;

$D_{high}(age, LC)$  is the average dose of high quality in the  $LC$  in question and age group in question.

3. One considers the distribution of values  $K(age, LC)$ , and one uses, as its characteristic, the robust estimate of its median. The median value  $K(age, LC)$  of distribution is used as correction factor to the calibration factor which was formerly used for the device with the serial number in question, if it differs more than by 30 % from 1.

This technique is intended for specifying the calibration factors both for SRP-68-01 devices with missing calibration data, and for spectrometric devices referred to Class 2 (Table 8.15.1).

#### Conclusions:

- The difference in doses calculated according to spectrometric and non spectrometric data is mainly due to lack of true device calibration factors and to their replacement by an average universal calibration factor for all SRP-68-01 devices..
- For Lists of measurements with SRP-68-01 devices with missing calibration data, one suggests to use device-specific or oblast-specific calibration factors. Use of device-specific or oblast-specific calibration factors allows to correct to a considerable degree the results of non spectrometric measurements.
- A technique has been developed for restoration of device-specific calibration factors for SRP-68-01 devices with a concrete serial number and missing calibration data. This technique provides for a procedure of comparative analysis of doses calculated on samples of the same type according to the results of measurements with devices having known calibration factors and the device tested. The application of this technique is planned for the following quarter of investigations.

# 8.18 PARTIAL COLLECTION OF THE DATA NECESSARY FOR ASSESSMENT OF DOSES OF EXTERNAL AND INTERNAL (FROM $^{137,134}\text{CS}$ ) EXPOSURES FOR THE MEMBERS OF COHORT. CREATION OF GEOCODED DB RADIOECOLOGICAL FEATURES FOR UKRAINE SETTLEMENTS FROM RAIONS UNDER STUDY.

The Laboratory of Dosimetry Models and Radiation Prognosis of the Department of Dosimetry and Radiation Hygiene has provided materials necessary for assessment of doses of external and internal exposure from radiocaesium isotopes. These data include:

- a) Reference values of  $^{137}\text{Cs}$  soil deposition on settlements' territories ;
- b) System of referent age-dependent behavior factors.
- c) System of referent transfer factors reflecting radiocaesium transfer from soil to the locally produced milk:
- d) Referent age-dependent alimentary rations of inhabitants;
- e) Referent function of changes in the time of standard milk equivalent of inhabitants' ration.

The data obtained for referent values of  $^{137}\text{Cs}$  soil deposition and for referent transfer factors have been geocoded and they represented a basis for calculation of doses of external gamma-exposure and internal exposure from radiocaesium for members of those cohorts for which one plans to obtain total thyroid exposure doses.

The referent values of density of  $^{137}\text{Cs}$  soil deposition ( $\sigma_{\text{Cs}}$ ) and of transfer factors ( $k_m$ ) were available for more than 99 % and 83 % from 637 settlements in raions under study, respectively (Table 8.18.1). For 3 settlements for the value  $\sigma_{\text{Cs}}$ , and for 100 settlements for the value  $k_m$ , these necessary parameters for obtaining dose estimates were found using the method of geostatistical interpolation procedure [1]. These parameters may be furtherly specified using additional information on direct measurements of  $^{137}\text{Cs}$  concentration in milk. Fig. 8.18.1 to 8.18.3 show spatial distribution of transfer factors "soil-milk" in the raions under study.

Information for settlements, which are not included in the number of settlements studied according to the Project, will be additionally used, as these settlements will be mentioned in personal questionnaires concerning the regime of behavior of cohort members.

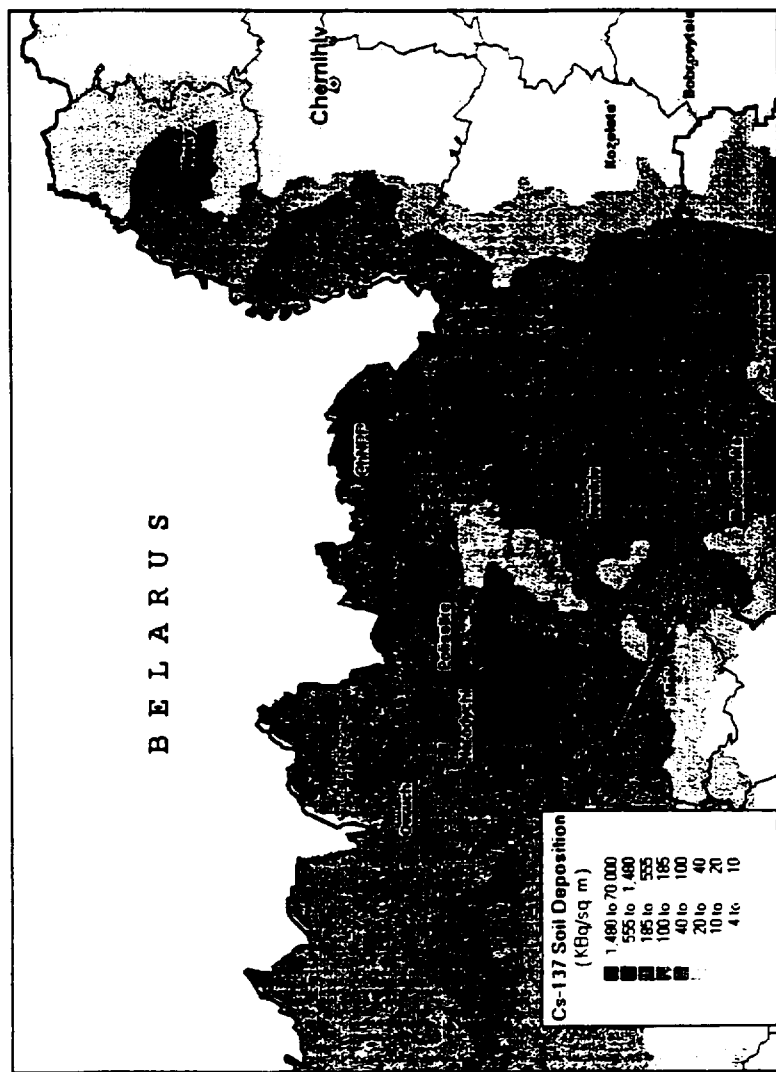
Furtherly, the question of the contribution of external gamma-exposure and internal exposure from radiocaesium for the inhabitants of Prypyat and 30-km zone is also to be answered. In order to

resolve this problem, it is necessary to use additional data on the dynamics of gamma dose-rate in Prypyat and 30-km zone. We plan to deal with this matter

Table 8.18.1. – Distribution of data on  $^{137}\text{Cs}$  soil contamination and estimates of  $^{137}\text{Cs}$  "soil-milk" transfer factors for 7 raions under study

Oblast	Raion	Number of settlements with data on $^{137}\text{Cs}$ soil contamination			Number of settlements with data on "soil-milk" transfer factors		
		Data on direct measurements	Reconstructed data	Total	Data based on direct measurements	Reconstructed data	Total
Kyivs'ka	Ivankivs'kyi	75	-	75	72	3	75
	Polis'skyi	40	1	41	25	16	41
Zhytomyr's'ka	Narodychs'kyi	73	-	73	55	18	73
	Ovruch's'kyi	134	2	136	128	8	136
Chernihiv's'ka	Kozelets'kyi	101	-	101	77	24	101
	Ripkins'kyi	105	-	105	92	13	105
	Chernihivs'kyi	106	-	106	88	18	106
Total		634	3	637	537	100	637

Figure. 8.18.1.  $^{137}\text{Cs}$  soil deposition in study area



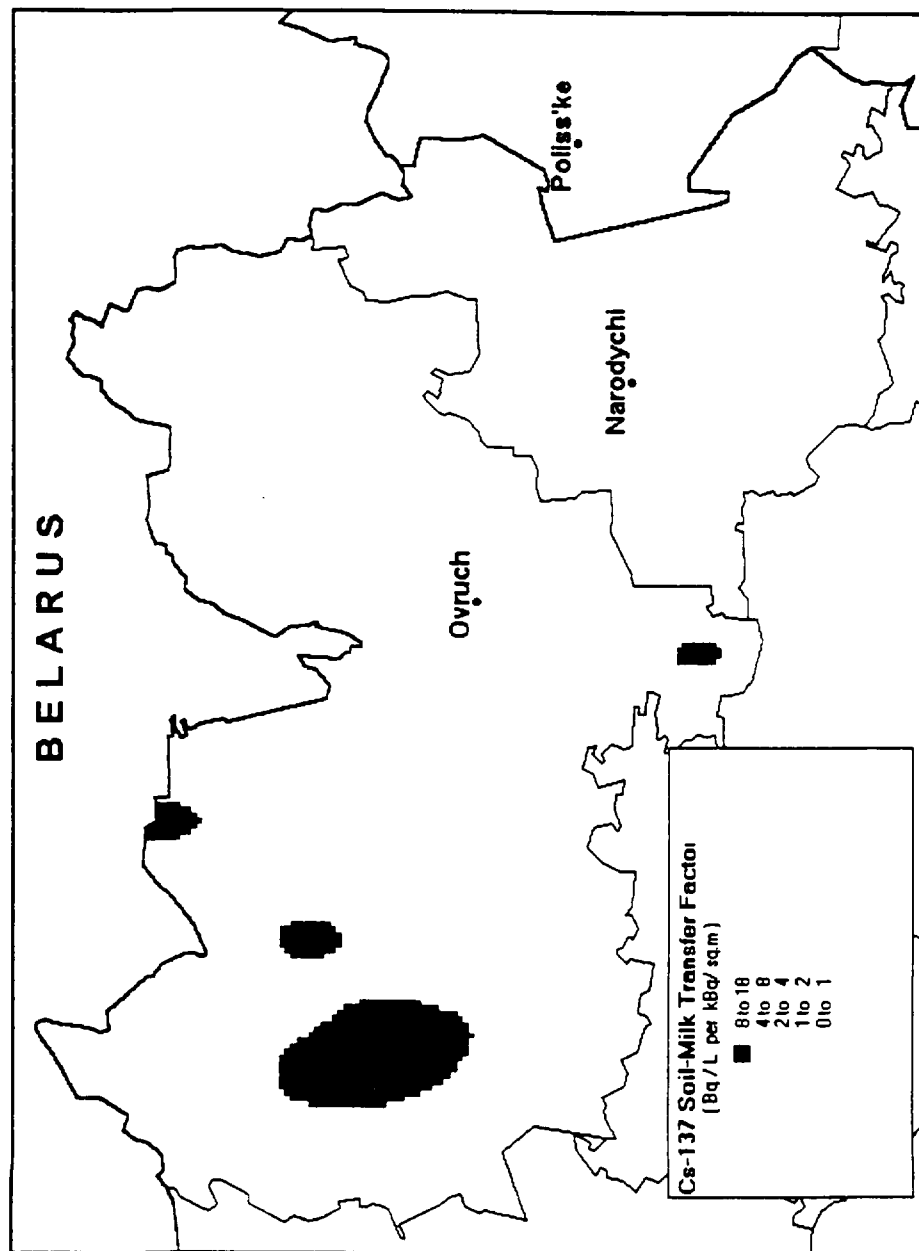
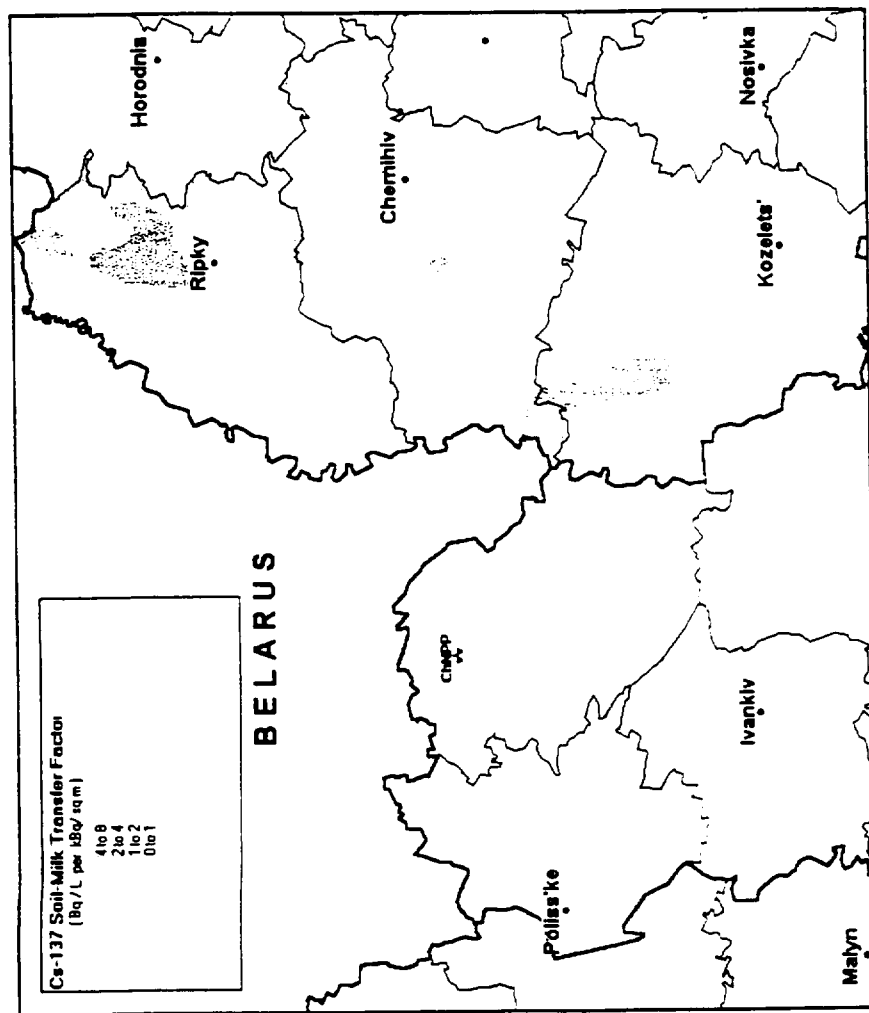


Figure 8.18.2. Spatial distribution of  $^{137}\text{Cs}$  soil-milk transfer factors in Narodychs'kyi and Ovruch's'kyi raions.

Figure 8.18.2.  
Spatial distribution  
of  $^{137}\text{Cs}$  soil-milk  
transfer factors in  
Ivankivs'kyi,  
Polis'skyi,  
Kozelets'kyi,  
Ripkins'kyi and  
Chernihivs'kyi  
raions



SIMULTANEOUSLY WITH ASSESSMENT OF THE CONTRIBUTION OF SHORT-LIVED IODINE ISOTOPES FOR THIS SUBCOHORT.

A preliminary assessment of the total dose of internal exposure from radiocaesium and external gamma-exposure for the period 1986 to 1997 has been made for more than 2000 rural settlements located in Kyivs'ka and Zhytomyrs'ka oblasts. The technique of assessment of the total thyroid dose accumulated for 11 years from other than  $^{131}\text{I}$  sources of exposure, is described in the previous report (milestones 8.16 and 8.17), as well as in publications [2-5]. This dose is compared to estimates of average age-dependent doses of thyroid exposure from  $^{131}\text{I}$  in the same settlements. Summing up of equivalent thyroid exposure doses from iodine radioisotopes with equivalent doses of external and internal exposure of this organ at the expense of "caesium" component is admissible, since in the latter case a uniform exposure of all organs and tissues, and therefore of thyroid gland, takes place.

The average contribution of the total dose of external gamma-exposure and internal exposure from radiocaesium, expressed in per cent to the average thyroid exposure dose from  $^{131}\text{I}$ , is presented in Table 8.15.2 for three levels of exposure of this organ and three age cohorts. The results point out that the total dose from external gamma-exposure and internal exposure from radiocaesium provides from 0.3% to 0.6% from the iodine dose for the inhabitants of villages, and this part is increasing with age, but it depends to a small degree on the level of iodine exposure.

Table 8.18.2. -Total Chernobyl dose due to external gamma-exposure and internal exposure to  $^{137}\text{I}$ ,  $^{134}\text{Cs}$  obtained by residents of rural settlements during 1986-1997 (percent to  $^{131}\text{I}$  thyroid dose)

Age groups (years of birth)	Total dose due to external and internal $^{137}\text{I}$ , $^{134}\text{Cs}$ thyroid exposure for different levels of $^{131}\text{I}$ thyroid exposure		
	<0.1Gy	0.1-1Gy	>1 Gy
1986	0.27%	0.53%	0.58%
1975-1978	2.3%	3.5%	2.1%
1968-1970	5.6%	6.0%	3.9%

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Appendix 1

Dynamics of invitation of patients to the screening

\_\_\_\_\_ oblast, \_\_\_\_\_ raion,  
 \_\_\_\_\_ selskiy sovet \_\_\_\_\_ settlement,  
 \_\_\_\_\_ Surname of the person filled in the  
 form

1. ID	2. Surn ame	3. Na me	4. Patr ony mic	5. Last known Address	6. Date of initia l cont act	7. R es ult	8. Reas on for the refus al	9. New addre ss of patien t, if know n	10. Date of repe ated cont act	11. Re sult	12. Com ment

Instruction on filling in the table "Dynamics of invitation of patients to the screening"

1. In the field 7 "result " should be put the following codes

1-, if the patient came for screening,

2-, if the patient agreed to come for screening but didn't show up

3-, if the patient refused to come in suggested time

4-, if the patient definitely refused to participate in screening

5 -, patient left (if so, please, in the field 'new address' state new place of dwelling)

6 -, if the patient left, but there still live relatives, able to send to the patients information about screening

7 -, patient is not found

8 -, patients died

2. Possible reasons for refusal (field 8) are written as following codes;

1-, patient couldn't afford trip to the place of screening

2-, patient couldn't find time for examination

3-, patient is not interested in his health condition and he didn't want to be under the screening in Project

4-, recently was examined under other programs

5-, afraid of drawing the blood

6-, reason of refusal is unknown

7-, other (mention in the field 'Comments')

**UKRAINIAN - AMERICAN SCIENTIFIC PROJECT ON THE STUDY  
OF CANCER AND OTHER THYROID DISEASES  
IN UKRAINE FOLLOWING THE CHORNOBYL ACCIDENT**

Tasks for the 3rd quarter of the 3rd year (December 1998 – February 1999)

	TASK	man*m onth
	<b>Management and administration</b>	
1.14	To organize screening of cohort members residing in Kozelets raion of Chernihiv oblast on the base of the Clinic of the Institute of Endocrinology and Metabolism of the Acad.Med.Sci. Ukraine, by fixed team.	0.5
1.15	To perform a work in order to use databases of oblast and raion departments of passport registration and migration work of Kyiv, Chernihiv, Zhytomyr oblasts, and of corresponding Department of the Ministry of Internal Affairs of Ukraine in order to specify addresses of residence of potential cohort members.	0.5
1.16	To organize a regular meeting devoted to Project implementation (Ministry of Public Health of Ukraine, administration and participants in the Project).	1.0
1.17	To prepare customs clearance documentation for shipments which arrive in the framework of the Project, and to receive these shipments.	2.0
	<b>Establishment of the cohort</b>	
2.10.	To find addresses of possible cohort members with were resettled for Chornobyl and raion, Pripjat, Poleskiy rayon to other oblast of Ukraine using database of Kyiv oblast healthcare system and oblast passport office.	2.0
2.11.	To identify settlements with substantial number of patients, resettled from contaminated areas and clarify a possibility of their examining.	2.0
	<b>Invitation of patients for endocrinologic screening</b>	
3.1	To finish invitations by the telephone of the cohort members currently living in Kyiv which were resettled from Chornobyl and Prypyat.	1.0
3.6	To finish examination of study subjects who currently live in Ovruch raion, Zhitomir oblast.	1.0
3.10	To obtain consent to take part in screening from cohort members who reside in Narodichi raion, Zhitomir oblast.	1.0
3.11	To obtain and analyze information on study subjects who didn't come for examination in Ovruch rain, Zhitomir Oblast	1.0
	<b>Endocrinologic examination of the subjects</b>	
4.6	To perform screening by mobile teams of cohort members residing in Narodychi raion of Zhytomyr oblast.	21.0
4.7	To perform screening by fixed team, on the base of the Institute of	21.0

	Endocrinology and Metabolism, of cohort members residing in Kozelets raion of Chernihiv oblast.	
<b>Operation of the Central Laboratory</b>		
5.2	To perform all laboratory investigations in the process of screening.	7.0
<b>Operation of Data Coordinating Center</b>		
6.15.	To develop software for image processing and introduction from magneto-optical disks into Project database.	1.0
6.16.	To continue data input from Locator Forms into Project database.	5.0
6.17.	To develop software for data input from primary Registration Form.	2.0
6.18.	To transfer available software to SQL platform.	1.0
<b>Pathology support for diagnosis of various forms of thyroid pathology.</b>		
7.1.	To continue collection and pathology examination of morphologic material from all patients born in 1968 and later from cohort oblasts and having been operated at the Institute of Endocrinology and Metabolism for different thyroid diagnoses.	6.0
7.2	Preparation of additional histological specimens for the morphologic data bank of the Ukr.-Am. Project (after identification of concrete patients included in the cohort).	1.0
7.3	To ensure intraoperational diagnosis, histological processing and pathomorphologic analysis of specimens obtained from patients selected for surgery after screening. Preparation of additional histological specimens for the morphologic data bank of the Ukr.-Am. Project.	1.0
7.4	To fill in the Pathology Forms for the patients with revealed cases of thyroid pathology, included in the cohort under study. To set these data into computer and provide them to DCC (after development of an appropriate computer program by DCC staff).	1.0
<b>Dosimetry support of the Project</b>		
8.15	Verification of calibration factors on the base of the technique for retrospective assessment of "device"-specific ("list"-specific where it is possible) calibration coefficients.	8.0
8.7.	To continue the support of the questionnaire DB. Establish, augment, and maintain database of personal questionnaire data for cohort members.	12.0
8.19.	Incorporation of information on date and duration of fallout.	8.0
8.20.	Estimation of age-dependent background incidence rate for cohort under the follow-up	4.0
8.21	Practical approval of probabilistic computerized record linkage program on dosimetric data.	2.0

Dr. V.A.Stezhko  
Director, BelAm Project,



## REPORT

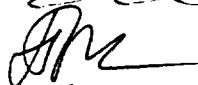
**Medical-Biological, Epidemiological, Dosimetical, Computer-Informational, Administrative Activities for Implementation of Joint BelAm Scientific Protocol for the Studies of Thyroid Cancer and Other Thyroid Diseases in Belarus Following the Chernobyl Accident in the Framework of Invoice for the period of 01.10.1998 - 31.12.1998**

**VICE-DIRECTOR ON CLINIC  
SCREENING CENTER**



**V.A. RZHEUTSKY**

**QUALITY CONTROL GROUP**



**O.N. POLIANSKAJA**

**DATA COORDINATING CENTER**



**N.R. LESNIKOVA**

**DOZIMETRICAL GROUP**



**V.F. MINENKO**

**EPIDEMIOLOGICAL GROUP**



**E.E. BUGLOVA**

**CENTRAL LABORATORY**



**S.V. PETRENKO**

**MINSK, 1998**

**Task No. 1: The management and administration of the BelAm Thyroid Study.**

**Milestone 1: Weekly meetings with the group leaders to discuss and record the progress of the Project and their reflection in the minutes.**

*(Administrative group)*

In the fourth quarter Administrative Group conducted 12 meetings with Project Group Leaders. During these meetings Leaders reported for performed activity of their groups in the 4-th quarter. All the scheduled measures have been fulfilled..

Special meeting was dedicated to problem of quarter reports compiling. It was recommended to the Group Leaders to be more exact and detailed while formulating performed activity.

The question was also discussed regarding reconstruction of spaces for screening group. The reconstruction is going on according to the schedule. In the 1-st quarter 1999 it is expected to finish up the reconstruction.

The following questions have been also discussed at the meetings:

1. Set up an archive of hard copies. It was decided to store all hard copies in board-boxes before file cabinets will be purchased.
2. Share information with Gamely Dispensary cooperating with Sasakava Foundation. Data on 4.5K individuals examined in Sasakava Project will be given to BelAm Project as soon as computer data base will be set up. At present programs for data entry are at the process of installation.
3. Schedule cohort selection. Dr. Buglova was charged to get information of subjects addresses from local institutions of Ministry of Home Affairs. The information have been received. Screening schedule for January and February 1999 is in progress now
4. Update Operational Manual. Group Leaders have worked out their suggestions for changing of Operational Manual. Chief of Quality Control Group is in charge for changes to Operational Manual.
5. Train staff in accordance with the rules of activity performance in the Project. Training have been performed. Records of training are kept by Quality Control Leader and in Groups.
6. Provide Central Laboratory with reagents. It was noted that there is no regular deliveries of reagents for estimation of hormones and antibodies. Dr. Petrenko was charged to prepare detailed request for 1999 deliveries and send it to NCI. The request form has been sent.
7. Trip of mobile team to Khojniki. It was decided to send invitations to subjects to come to Khojniki Regional Hospital in December. Mobile team of 12 specialists worked in Khojniki from 14 to 22 December. 174 subjects have been examined.
8. Participate in data linkage workshop in Kiev. Head of DCC, representatives of Cancer Registry and Chernobyl Registry participated in the workshop. Mrs. Lesnikova reported about the results of the workshop. It was also discussed the Project experience of Kiev Research Institute of Endocrinology.

9. Formalization of diagnosis of thyroid diseases. Drs. Danilova and Polianskaja have prepared suggestions on algorithm of diagnosis formulating for physicians and on reference for data entry operators..

Among discussed questions there were also questions regarding equipment repair, acquisition of expenditures, and other current issues.

**Milestone 2: Administrative support of cohort establishment to supply access to various informational sources, especially sources of address information.**

*(Administrative group)*

For the reported period Administrative Group provided administrative assistance in getting address information for individuals moved to another places of residence following the accident. Administrative group found money to purchase expenditures. At the cost of Research Institute of Radiation Medicine and Endocrinology it was bought paper, toner, cartridges. It was arrange a transportation of mobile team and field trip of epidemiologists, dosimetrists, and screening team. Administrative group arrange contacts with Passport Offices, Ministry of Home Affairs.

Administrative support was provided to patients referral from the rajons. As well as some preparatory activity was performed for subjects examination in Khojniki.

**Milestone 3: Coordination between Belarus and U.S. participants with respect to all activities of the Project.**

*(Administrative group)*

All the activities of the Project were coordinated according to the following aspects:

1. Compiling of quarter reports. It was agreed to compile short reports describing all the tasks and milestones scheduled for the quarter.
2. Equipment repair. ABBOT instrument have been fixed. Question of payment for fixing of ultrasound probe is to be decided.
3. Acquisition of equipment, reagents and expenditures. Paper, toners, cartridges, computers have been purchased by American colleagues during their staying in Minsk, October 1998. A specified schedule of deliveries for 1999 have been prepared.
4. Appointment of Head of Quality Control Group. Dr. O.N. Polianskaja has been appointed to this position.
5. Personnel. Mrs. N.R. Lesnikova has been appointed to the position of DCC Head. Mr. A.V. Kuvshinnikov has been retired from the position of DCC Head and he works in Project as an advisor for computer aspects and is responsible for equipment utilization.
6. Brest file. Information of thyroid direct measurements in population of Brest Oblast occurred to be lost.
7. Meeting of bi-national Advisory Group. The meeting is scheduled for 1999.
8. Multiple visas. All necessary information have been sent to NCI.
9. Joint work of Belarus specialists and US experts. It was decided that in 1999 such work will be performed with small groups..

**Task No. 2: The establishment of the cohort of subjects for study.**

**Milestone 4: Work to locate provisional cohort of 15.000 and select at least 1.000 accessible to the Minsk Dispensary**

*(Data Coordinating Center)*

*(Epidemiology Group)*

In the IV-th quarter (01.10.98.–31.12.98r) Epidemiology group completed searching of subjects included to the cohort through Address Offices of six oblasts of Belarus.. DCC set lists of provisional cohort subjects who according to previous information lived in Minsk and Minsk oblast and had status “no response within a month”, “wrong address”. Besides this file contains information on subjects who according to different sources moved to Minsk or Minsk oblast without exact address information, and all the subjects who according to dosimetric DB lived in Minsk or Minsk oblast at the moment of Chernobyl accident and had not been located in the initial search.

Epi Group sent a list of 1622 subjects to Address Offices of Minsk and Minsk Oblast. As a result of this activity 586 new addresses (36,1%) have been entered to mailing system of epidemiological base for sending invitations to examination scheduled for November of current year.

To verify addresses of children born 1982-1986 who is under 16 and could not be registered themselves in Address Offices Epi Group put the following task to DCC: to perform a selection of pairs considering their place of residence at the time of the accident according to the following parameters: family name of child and similar family names of provisional mothers. As a result of performed activity DCC create a file comprising 988 children and 4.784 mothers who lived in Gomel Oblast at the time of the accident. An attempt was made to define address of this group of children through address of provisional mother. Epi Group has sent a list to Address Office of Gomel Oblast.

For the reported period DCC made a preliminary review of possibility of additional subjects selection in total base of 39 K. For this purpose computer linkage was performed between DB of direct measurements and following DBs

- Chernobyl Registry,
- Polyclinics ## 32 and 25, Minsk city,
- Sasakava Foundation,
- WHO,
- National Dispensary of Radiation Medicine,

As a result of performed linkage 4.703 addresses have been obtained. This information was sent to Dr. Beebe for discussion.

**Milestone 5: Determine current addresses of about 5,000 members of cohort for whom letters were sent and who did not respond.**

*(Epidemiology Group)*

Location of subjects not responded to invitation was continued in the 4-th quarter. Searching activity was performed through Address Offices of Minsk and Minsk Oblast and 3 Departments of Public Education (DPE) of Gomel oblast. The results of this activity are presented in Table 1.

**Table 1. Results of address verification of provisional cohort subjects not responded the invitational letters**

<i>Result of searching activity</i>	<b>Number of subjects, abs. %</b>		
	<i>Address Office</i>	<i>DPE, Gomel oblast</i>	<i>Total</i>
New address	586 (36,1%)	42 (3,5 %)	628 (22,2 %)
Confirmed former address	75 (4,6 %)	103 (8,5 %)	178 (6,3 %)
Moved within Belarus	12 (0,74%)	80 (6,6 %)	92 (3,3 %)
Moved out of Belarus	6 (0,4 %)	15 (1,2 %)	21 (0,7 %)
Death	1 (0,06 %)	-	1 (0,03 %)
Imprisoned	3 (0,2 %)	2 (0,2 %)	5 (0,2 %)
Lack of information	917 (56,5 %)	948 (78,5 %)	1865 (65,9 %)
Not reside verified address	18 (1,1 %)	17 (1,4 %)	35 (1,2 %)
Disagreement with DBDM	4 (0,3 %)	-	4 (0,1 %)
<b>Total:</b>	<b>1622 (100 %)</b>	<b>1207 (100%)</b>	<b>2829 (100 %)</b>

As a result of performed activity to 628 provisional cohort subjects informational letters with invitation to examination have been sent. 31 individuals have been excluded from further search (moved out of country, died, not fitted by age, imprisoned), 103 individuals (children of school age living in Gomel Oblast) are included to reserve group for examination by mobile team of Minsk Dispensary, to 75 subjects living in Minsk and Minsk Oblast who's address was confirmed by Address Office repeated invitations have been sent.

**Milestone 6: Determine the location of geographical areas with high numbers of people with identified current addresses for possible examination by mobile teams**

*(Epidemiology Group)*

*(Data coordinating Center)*

To get the information of geographic distribution of cohort subjects of children age that could be examined by mobile team the lists have been sent to 10 DPE of Gomel oblast in 3-rd quarter. In the 4-th quarter we have received information from Bragin, Narovlia, and Bragin DPEs. Information of verified addresses is presented in Table 2

**Table 2. Results of searching activity of cohort subjects from high dose and randomized groups through DPE, Gomel oblast**

<i>Results of search</i>	<b>Number of subjects, abs.</b>			
	<b>Vetka</b>	<b>Narovlia</b>	<b>Bragin</b>	<b>Total</b>
New address	24	5	13	42
Confirmed former address	18	53	32	103
Moved within Belarus	24	40	16	80
Not reside verified address	-	15	2	17
Moved out of Belarus	6	9	-	15
Imprisoned	-	-	2	2
Lack of information	109	205	634	948
<b>Total:</b>	<b>181</b>	<b>327</b>	<b>699</b>	<b>1207</b>

Performed by Epi Group activity allowed to define new addresses of 42 children and verify addresses of 120 provisional cohort subjects (confirmed address, moved out of Belarus, imprisoned). Thus 145 individuals living in Bragin, Vetka, and Narovlia rajons could be examined by mobile team of Minsk Dispensary.

In the 4-th quarter at the stage of invitation of subjects to be examined by mobile team in Khojniki DCC set up a file of 724 individuals who had statuses of "no response within a month" or "reserve". Address information was preliminary verified through Address Office and DPE. To 542 individuals living mostly in Khojniki (371 inds.) invitations to examination have been sent. Additional list of 182 provisional cohort subjects who had status "no response within a month" (rural inhabitants) was used by epidemiologists for addresses verification through local obstetrical stations of Khojniki rajon. During field trip of mobile team to Khojniki Epi Group worked with provisional cohort subjects of these two lists. To make a contact with cohort subjects epidemiologists visited 189 apartments, Technical School #131, Comprehensive Schools #1,2,3,4, assisted in delivery of subjects from villages Malishev and Sudkovo to examination. As a result of performed epidemiological activity it was revealed the following: from the whole number of individual to whom invitations have been sent 5 inds. Moved out of Belarus, 47 - wrong addresses, 10 inds. could not come to examination because of military service, pregnancy, treatment in sanatorium, study. While verifying addresses of provisional cohort subjects from Alecsichi, Vit', Ezapov, Gubarevichi, Malishev, Partizanskaja, Poselichi, Rabets, Rudakov, Slobozhanka, Strelichev and Sudkovo villages who did not respond to previous invitations it was find out that 13 of them moved to new place within Belarus, 15 - wrong addresses, to 3 of them "reserve" status was given, and one individual is imprisoned. 25 subjects agreed to be examined by mobile team. Totally, 174 provisional cohort subjects have been examined by mobile team, 133 of them (76%) had previous status "no response within a month" and 41 had "reserve" status. High percentage of no-respondents among examined by mobile team confirms the possibility of involving mentioned subjects to cohort with the help of mobile team.

**Milestone 7: Create initial data base of exposed "in utero"**  
(Epidemiology Group)

In the 4-th quarter epi group continued the activity aimed at setting up initial DB of cohort study of children born 26.04.86 - 31.01.87 and exposed "in utero". In the fourth quarter information on 12.900 inds. was entered to the DB. By now this file comprise information on 28 K of children exposed "in utero".

**Task 3. The invitation and scheduling of subjects for endocrinologic examination**

**Milestone 9: Preparation of the letters of invitation, software and procedures for inviting and scheduling subjects for examination**  
(Epidemiology Group)

In the 4-th quarter epi group sent 2065 informational letters with invitation to examination. 248 subjects have been invited for October who's addresses were verified through Address Offices and DPE. In November invitations have been sent to 807 provisional cohort subjects who according to the data of Address Office live in Minsk or Minsk Oblast (597 inds.) and in other Oblasts of Belarus (210 inds.). For December the following groups of subjects have been invited: 445 cohort subjects for annual follow up

examination in the National Dispensary (follow up visit), 23 inds. for initial visit (their addresses have been verified in the 3-rd quarter through DPE of Gomel Oblast), and 542 inds. for examination by mobile team (they have status “no response within a month” and live in Khojniki and Khojniki rajon).

For reported period 2.362 forms have been entered to epidemiological DB of cohort study, 1.357 of them have been entered in automatic mode.

*((Data Coordinating Center))*

In the fourth quarter DCC started working on reconstruction of the history of subjects searching through different sources. Up till now some part of searching results have not been entered to the DB because information was stored in separate files, and computer data processing system has not been developed.

For the reported period an algorithm and a part of software have been designed that allowed to keep the history of subjects searching, results of searching activity, and to combine it with existing epidemiological dB tracing current state of cohort as well as procedures of visits scheduling and invitation of subjects to examination. Such efforts will also allow to decrease a group of “no response within a month and to increase number of subjects invited to examination.

Algorithm for automatization of searching system is presented in Fig 1. Because of importance of questions related to cohort maintenance DCC have worked out software used for greeting of subjects with different holidays and all subjects passed examination received New Year greetings.

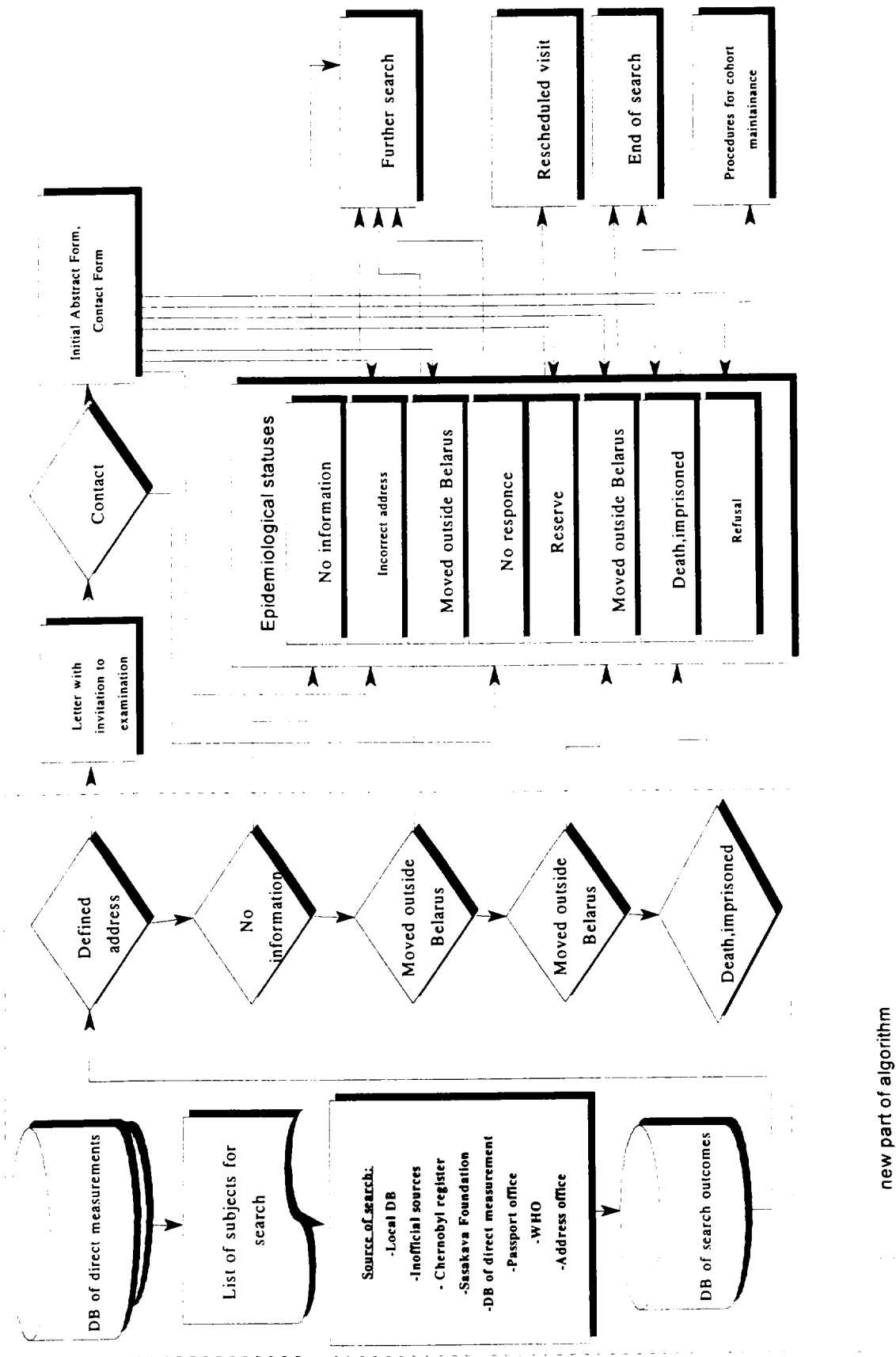


Fig.1. Algorithm of search and making contact with provisional cohort subject

**Task No. 4 The endocrinologic examination of subjects, including subsequent diagnostic procedures leading to the establishment of the final pathologic diagnosis.**

**Milestone 9: Screening up to 600 subjects in Minsk Dispensary, including the laboratory work.**

***(Screening Center)***

**Examination.** Totally, for the reported period 591 inds. passed examination in the Screening Center: 465 (78.7%) - for the first time, and 126 (21.2%) - repeated. Mobile team examined 174 inds. (29.44%) in Khojniki (December 10-23, 1998).

From all examined subjects (591) in **69 (11.7%)** thyroid pathology have been revealed, in 16 of them (2.7%) - for the first time. Distribution of subjects according to revealed diagnosis is given below.

Thyroid cancer have been found in **8 (1.4%)** subjects. 2 of them (0.3%) the disease have been diagnosed for the first time, and in both of them - while repeated examination

1. L.I. Stelmack, born 1973., previous diagnosis - nodular goiter repeated examination - 22.10.98. Fine needle biopsy (FNB) of thyroid was performed, cytogram revealed the cells of papillary cancer. Hospitalization to the Clinic, Research Clinical Institute of Radiation Medicine and Endocrinology (RCIRME) - 29.10.98-05.11.98. Surgery in National Center of Thyroid Oncopathology (NCTOP) - 23.11.98 (pT1aNoMo - according to the data of NCTOP). From the moment of screening examination to the moment of surgery 1 month have passed.
2. T.S. Tselujko born 1984 , previous diagnosis - nodular goiter, repeated examination - 08.12.98. Fine needle biopsy (FNB) of thyroid was performed, cytogram revealed the cells of papillary cancer. Hospitalization to the Clinic, Research Clinical Institute of Radiation Medicine and Endocrinology (RCIRME) - 16.12.98-24.12.98. Surgery in National Center of Thyroid Oncopathology (NCTOP) - 05.01.99 (pT2aN1aMo - according to the data of NCTOP). From the moment of screening examination to the moment of surgery 1 month have passed.

In both cases while repeated examination according to ultrasound data change of structure and fast enlargement in sizes of previously revealed thyroid malformations have been revealed. Such dynamics allowed to suspect thyroid cancer that was confirmed by thyroid FNB findings, and furthermore - by pathomorphological examination. The rest 6 cases of thyroid cancer have been revealed previously, 3 of them have been examined by the project initially and 3 - have passed repeated examination.

Diagnosis of nodular goiter at the stage of screening have been revealed in **33 inds. (5.5%)**. In 10 (1.7%) of the disease was revealed for the first time ( 9 - during initial examination and 1 - during repeated). In 23 subjects diagnosis was known previously (17 - examined initially). Besides, in **4 (0.7%)** inds nodular goiter have been suspected.

By the time of this report submittal endocrinological department have examined 12 from 33 patients with nodular goiter. The diagnosis was confirmed in 2 from 4 patients with suspicion to it.

**6 inds.(1%)** have been examined with diagnosis of autoimmune thyroiditis. 3 of them have been diagnosed for the first time.

Besides **5 (0.9%)** inds. have been examined with suspicion to autoimmune thyroiditis. In 4 of them the diagnosis have been confirmed in the Clinic RCIRME. 1 patient is scheduled to hospitalization for 1-st quarter 1999.

**11 inds.(1.9%)** have been examined with diffusive goiter IB. For the first time this disease have been revealed in 2 subjects (both during initial examination), previously known disease was in 9 inds. (6 of them have been examined initially). 2 inds. (0,3%) have been examined with diagnosis diffusive goiter, II degree (both of them have repeated examination).

Thus, the structure of thyroid pathology revealed in the 4-th quarter was the following:

Thyroid cancer	8	(11.6%)
Nodular goiter	37	(53.6%)
Autoimmune thyroiditis	11	(15.9%)
Diffusive goiter, 1B и 2 degrees	13	(18.9%)

As it is seen from given data the priority is for nodular goiter (53.6%).

**Referral to thyroid FNB.** At the screening stage 6 FNB have been performed for the patients with nodular pathologies. All the punctures were informative. Distribution of patient according to FNB results is the following: thyroid cancer -2, nodular goiter - 3, without changes - 1.

**Referral to hospitalization.** In the fourth quarter 44 subjects have been examined in the Clinic, RCIRMEчеловека: 20 children, 22 adults. 4 subjects have been consulted in NCTOP, 3 of them have been operated (2 - thyroid cancer, 1 - colloid-cystal goiter) One subject with previously revealed thyroid cancer had no signs of recedive and metastases..

**Final Medical Conclusion and Recommendations.** In the 4-th quarter Screening Center received from the Central Laboratory the following tests results: blood test - 1.041 indices, TSH - 155, Ab to TPO - 740, Ab to TG - 897, Calcium - 170, Parathyroid Hormone - 39. Thus, final diagnosis was made to 155 subjects. Screening Center has not received the results of iodine content in urine of subjects.

**(Central Laboratory)**

In the 4-th quarter Central Laboratory examined 597 subjects. The results of the Central Laboratory activity in the 4-th quarter:

- taken blood samples - 596
- filled forms of blood collection - 596
- refused from blood collection - 1
- taken urine samples - 592
- filled forms of urine collection - 597
- refused from urine collection - 5

Performed tests:

1. Content of TSH hormone- 594
2. Content of ionized Calcium- 594
3. Content of Iodine in urine - 580
4. Content of antibodies to TG - 510 (for 1-st and 2-nd quarters 1998)

5. Content of antibodies to TPO - 510 (for 1-st and 2-nd quarters 1998)

6. Content of parathyroid hormone - has not been estimated

Tests of thyroglobuline were not performed because of lack of reagents.

#### **Estimation of functional state of parathyroid glands through the level of ionize calcium in blood serum**

Estimation of ionized calcium was performed in blood serum of 594 cohort subjects. During the preliminary studies a value of regional norm was obtained (random sample of 150 healthy inds.) -  $1,26 \pm 0,005$  ( $M \pm \sigma_2$ ) mMol/l, range of distribution: 1,1 - 1,35 mMol/l. These finding of regional norm were taken as a control index of ionized calcium content in blood while reviewing the results of examination of cohort subjects. While making an individual review of calcium in examined cohort (594 inds.) 8 subjects (1,35%) had increased content of given index. Obtained data need to be further studied and need further examination of the cohort subjects. In particular, they should be subjected to examination of parathyroid hormone by radioimmunal method. Obtained data are entered to the "Paradox" DB for further reviewing.

#### **Estimation of thyroid functional state through the level of TSH in blood and iodine excretion with urine.**

TSH content have been estimated in blood serum of 594 cohort subjects. In 5 subjects (0,84%) decreased level of TSH in Blood serum have been revealed, in 4 subjects (0,67%) increased level of TSH have been found. Because of two months delay in TSH reagents delivery (reagents have been received on 21 December, 1998) blood serums of subjects come to examination in the forth quarter have been analyzed and are entered to DB and to the Forms of blood collection and processing. Obtained results of TSH in blood will passed to the Sceening Center by January 20, 1999.

#### **Estimation of autoimmunal status of the body to thyroid proteins through the level of antibodies to TG and TPO in blood serum.**

Central laboratory performed an estimation of antibodies to TG and TPO in blood serum of 510 cohort subjects examined in the 1-st and 2-nd quarters of 1998 as antibodies reagents were delivered in August 1998 and could not be used because of limited expiration date in November - December 1998. Obtained results are entered to "Paradox" DB for further reviewing, to Forms of blood collection and processing.

In the 4-th quarter Central Laboratory entered Forms of urine collection and processing for 1.057 subjects, and Forms of blood collection and processing for 175 patients.

#### **Shortcomings**

Significant shortcoming is irregular delivery of reagents for estimation of thyroid hormones and antibodies to them in 1997 - 1998. Deliveries come with two or more months delay. Unfortunately, the problem of regular delivery is still unsolved.

Irregular deliveries lead to incomplete laboratory examination of the subjects and made impossible to put final diagnosis of thyroid disease and perform scientific review.

## **Milestone 10: Clinical Examination and Verification of Diagnosis in Patients with revealed pathology**

*(Quality Control Group)*

### **Examination in Endocrinological Department of Clinic, RCIRME.**

According to the results of screening by 01.01.99 46 inds. (7.8% from total number of examined) were hospitalized to Endocrinological Department of Clinic, RCIRME. Distribution of patient according to the final diagnosis is presented in Table 3.

**Table 3.**

**Distribution of subjects according to final diagnosis made in endocrinological department of Clinic, RCIPME.**

IDC	Nosologic form	## of subjects, abs. %	
193.0	thyroid cancer, state following surgical and (or) combined treatment	6	13
241.0	nodular nontoxic goiter	22	47.8
241.1	multinodular nontoxic goiter	9	19.6
245.2	autoimmune thyroiditis	5	10.8
242.0	diffusive toxic goiter	1	2.2
	post-surgical hypothyroiditis	1	2.2
	operated thyroid	1	2.2
	paratracheal cyst	1	2.2
	total	46	100

As it is shown from presented data nodular non-toxic goiter prevails in the structure of pathology of hospitalized patients. From 22 subjects with such diagnosis 4 inds have been referred to NCTOP for surgical treatment, three of them with suspicion to thyroid cancer (T.S. Tselujlo, L.I. Stelmack, V.V. Shevchenko) and one with thyroid adenoma N.A. Krotov)

At the clinical stage 15 thyroid FNB have been performed.

Deviations in final clinical diagnosis (D2) and screening diagnosis (D1) took place in 3 subjects

	(D-1)	(D-2)
D.A. Nikolaenko.A.	Diffusive goiter	Nodular goiter
T.V. Kirikova.	Diffusive goiter	Nodular goiter
A.G. Petrovsky.	Nodular goiter	Paratracheal cyst

By the time of report submitting two patients from four hospitalized in the 4-th quarter are still in the hospital

### **Hospitalization to NCTOP**

For the 4-th quarter 3 subjects have been hospitalized to NCTOP. All of them had surgical treatment: 2 - thyroid cancer (initially revealed), 1 - nodular goiter. 2 subjects (suspicion to thyroid cancer and thyroid adenoma) have not come to hospitalization.

**Milestone 11: Conduct the cytological and pathomorphological aspects of the Project.**  
***(Screening Center)***

For the reported period Project Cytologist examined 19 bioptates of subjects with thyroid nodular pathology. 105 slides have been reviewed. The results of this activity is the following: thyroid cancer - 4, suspicion to thyroid cancer - 1, atypical proliferation - 1, without pathology - 10, uninformative material - 3.

Updating of Cytological Form and Operational Manual was also performed. Now the question is to be decide regarding review of cytological materials stored in Clinic, RCIRME and NCTOP. Results of quality control of Cytological forms is presented in Milestone 12.

**Milestone 13: Expert support of screening activities**

***(Quality Control Group)***

Head of QC Group and expert-endocrinologist worked out a temporary manual for the Head of Screening Group with respect to questions not described in Operational Manual, i.e. criteria of conclusion "normal thyroid", rules for coding of nodular pathology and diagnosis under the question, procedure of patients treatment in terms not envisaged by Operational Manual, tracing of subjects who have not come to hospitalization.

For the reported period Head of QC Group reviewed 11 Pathomorphological Forms, 102 Hospitalization Forms, 31 Cytological Forms.

Review of Pathomorphological Forms showed that up till now patomorphologists use the form data from could not be entered to DB. It was also revealed that conclusions of pathomorphologists is in disagreement in some cases with conclusions of NCTOP in the main diagnosis and pTNM categories. There is also disagreement in number of revealed nodules according to the data of ultrasound examination (USE) and patomorphological examination (PME) (Table 4)

**Table 4.**

**Disagreement in diagnoses of Surgical Form. Pathomorphological, and Thyroid  
 Ultrasound Examination Forms**

ID	Subject Name	Main Diagnosis		P TNM		Number of thyroid nodules	
		NCTOP	BelAm	NCTOP	BelAm	USE	PME
76 389	V.E. Ivanov	Nodular goiter	Thyroid adenoma	-	-	-	-
115353	F.F. Kurlenko.	-	-	T2a	T4a	1	2
189112	Brel-Barash	-	-	No	Nx	-	-
178925	V.U. Koberko	-	-	T2a	T4	3	1
98 225	S.J. Marchuk	-	-	T2a	T4a		
110380	L,N. Danilchuk			N1b	N1a		

At the joint meeting with participation of surgeon and pathomorphologist these cases have been discussed. It was found out that disagreement in main diagnosis (thyroid adenoma and nodular goiter) was caused by atypical cases and could be solved by involvement of the third specialist-expert. Disagreement in pT4 and pT2 is caused by different interpretation of pT by pathomorphologists. Disagreements in pT1a and pT1b are also possible.

Review of disagreements in the number of nodules revealed during USE and PME is given below:

1. Subject Kurlenko: while PME a nodule has been found of 1mm not visualized in USE, that could be explained by resolution capacity of USE method.

Subject Koberko: according to USE data - three nodules in left lobe - nodule of cyst type of 2mm; and in right lobe - 2 nodules of complicated structure, 17 mm, one under another in mid and low part of a lobe. In PME nodule in left lobe has not been confirmed, and in right lobe - it was described as one nodule of similar size and location.

Expert analysis of thyroid FNB data and cytological examination showed that they could not be entered to computer because of lack of revised and adopted Form. New version of Form is reviewed by US expert.

Results of thyroid FNB performed at screening stage are presented in Table 5

**Table 5.**

**Distribution of subjects according to the results of thyroid FNB**

<b>Result of FNB</b>	<b>Number of subjects</b>	
	<b>abs. number</b>	<b>%</b>
<b>Not informative</b>	4	12.9
Without changes	10	32.3
Cancer, suspicion to cancer	8	25.8
Adenoma	1	3.2
Colloid goiter	7	22.6
Cyst	1	3.2
<b>Total</b>	<b>31</b>	<b>100</b>

As it is shown from the table a part of not informative FNB was 12.9%. This fact allows to estimate the work of physicians performed this activity as good. From 8 subjects with suspicion to thyroid cancer 5 had surgical treatment and cytological diagnosis was confirmed by PME.

It was revealed shortcomings in forms completion of two subjects to whom 2 nodule have been punctured and only one conclusion was made. Following revision of slides made by cytologist correction in corresponding forms was made. To simplify identification of number and location of puncturing nodules the Form is added by thyroid diagrams (D1, D2). It should be mentioned that the work of cytologist is complicated by absence of preliminary clinical diagnosis in the Form of thyroid FNB.

While making revision of Hospitalization Form it was revealed that information of this form is insufficient for cohort maintenance and tracing of subjects, as it was mentioned above. Besides, in Surgical Hospitalization Form there is a lack of information whether this surgery initial or repeated.

Experts perform their advisory activity at the base of Clinic, RCIRME. Totally, 10 subjects have been examined.

Expert of USE regularly perform quality control of examination. Some problems with recording of thyroid images to MOD have been revealed. They were caused by breakage of device for recording to MOD.

There were claims to the work of USE specialist in conditions of field trip. "SIGMA" instrument used for field trips could not be compared in quality of images with "TOSHIBA" instrument. Besides, because of lack of recording device not delivered by American side, recording of thyroid images to MOD have not been performed.

There was also performed expert estimation of configuration of thyroid images DB and its connection to screening DB.

Thus, QC Group participated in theoretical and practical aspects of the Project and performed advisory activity.

## **Task No. 5 Operational Manual and Project forms**

### **Milestone 13: Updating of the Operational Manual and study forms.**

#### ***(Quality Control Group and Heads of Project Units)***

Modernization of Operational Manual (OM) has been performed in following directions: edit of Russian version of the text, bring OM in accordance with actual procedure of examination, put necessary additions.

#### **1.2. Background**

Table Number of thyroid cancers annually revealed in children of Belarus from 1986 to 1997.

<b>Year</b>	<b>Number of Cases</b>
1986	1
1987	2
1988	4
1989	6
1990	28
1991	58
1992	65
1993	80
1994	80
1995	91
1996	84
1997	66

### **3.4. ABSTRACTING RECORDS BEFORE INITIAL CONTACT**

***(completely changed)***

To provide information that could be useful while making contact with cohort subjects, on each subject selected to the cohort preliminary demographic and identification information is collected. To obtain this information DCC use computer file of direct measurements DB. The following information should be collected on each subject:

- ◆ Family name, name, patronymic of a subject (if necessary, parents also);
- ◆ Year of birth;
- ◆ Address at 26.04.1986.

### 3.5. OBTAINING CURRENT ADDRESSES

*(Completely changed)*

Obtaining of such information will require constant and intensive work of Epi Group and DCC during first three years of study.

As soon as DCC set up a file a subjects for search the main task will be to find and confirm current address of a subject. Search of information I performed in two stages. The first one is the searching stage performing by DCC through the following sources of address information:

- ◆ DB of Chernobyl Registry;
- ◆ Local DBs (Polyclinics ## 25, 32 of Minsk; National Dispensary of Radiation Medicine; Clinical Hospital of Minsk Oblast, Gomel and Mogilev Dispensaries)
- ◆ File of Sasakava Foundation;
- ◆ Files of IPHECA WHO;
- ◆ DBs of registries of Gomel and Mogilev Oblasts.

Following stage of search is performed by Epi Group through the following sources of address information:

- ◆ Central Regional Hospitals (CRH);
- ◆ Regional Departments of Public Education (RDPE);
- ◆ Regional Passport Offices;
- ◆ Address offices (Ministry of Home Affairs of Oblast);
- ◆ "Summons for individuals evacuated from the areas of dangerous active contamination".

Search via mentioned sources is performed through formed lists or through collation of information on hard copies.

As soon as address or any other information that can describe the result of search or subjects' status in Project (no information, change of address, military service, death etc.) will be received the data are entered to epi DB.

To defined addresses letters are sent with the aim to make an initial contact with a subject, address verification and invitation to examination.

### 4.2. INITIAL CONTACT WITH STUDY SUBJECTS

*(Completely changed)*

Initial contact with STUDY subject is performed by Epi Group with the help from DCC. A family (or adult subject) will receive a letter from Epi Group on behalf of the Ministry of Health describing the study, its benefits to individual and suggesting a specific date and time of appointment. With the letter will be a pre-printed, stamped card to be mailed back to Epi group. It will provide for confirmation of the offered appointment, a request for an alternative or deferred appointment.. Besides, through the post card Epi Group verifies the date of birth, place of residence at the time of the accident and phone number where the

subject can be reached. Copies of letters and appointment confirmation card are in Appendix C-4-1.

As soon as post card come back to Epi Group Initial Abstract Form (demography) is completed to the subject. Given form is entered to the epidemiological DB of cohort study by Epi Group personnel. Initial Abstract Form and Instruction for its filling in are in Appendix A-3-1.

Based on the information of subjects preliminary consent to screening examination DCC prepares a Registration Log for specific period of time. Registration Log is passed to Screening Group. If a subject has not come to screening examination, a repeated letter of invitation is sent to him or a contact with him is made by telephone in order to clarify the reasons of patient's absence at examination and appoint him a new date of a visit. This activity is performed by Epi Group.

Following the repeated contact with the subject a Contact Form is entered to Epi DB. This form and instructions for filling in of electronic variant are in Appendix A-3-2.

#### **4.6. DOCUMENTING PARTICIPANT STATUS**

*(Completely changed)*

While setting up a file of epidemiological base of cohort study to each subject one of ten statuses (refusal, death, no response within a month, preliminary consent, moved out of the Republic, reserve, not fitted by age, preliminary consent for mobile team examination, imprisoned) The status is given on the base of

- ◆ data received from the source of address information while making verification of current subject's address while verifying subject's current address.;
- ◆ information from Post Card returned to Epi Group
- ◆ results of phone calls with the subject

Status is a dynamical characteristic of subject's state in the Project. Current status is entered to Epi DB. Using query system developed by DCC Epi Group makes an analysis of subjects' state in the Project in accordance with each status.

##### **4.2.1. HANDLING NON-RESPONSE**

*(completely changed)*

Data Coordinating Center together with Epi Group handles non-response. Non-response (lack of information) could appear at the following steps:

- ◆ locating of subject through different sources of address information;
- ◆ getting back a letter with post office note "individual does not reside given address";
- ◆ no response to a letter mailed to defined address.

In accordance with above mentioned steps the following subjects files are created:

1. Subjects who can not be located at the step of current address identification (through sources of information described in Section 3.5);
2. Subjects who have status "incorrect address";
3. Subjects who have status "no response within a month".

The work with subjects from the first and the second files is performed the following way. If searching of address was done not through all possible sources of information, the

search is continued through unused by now sources. Subjects whose address was verified through all known sources of information are combined in a separate file the work with which probably will require new sources of information or combination of sources used by now (i.e. search of children by mother's address through Address Office).

To subjects from the third file not responded to invitation within one month a second informational letter is sent. If there is no response to the repeated invitation a review is made through what sources of information address verification was performed. If subject was located through all possible sources of address information Epi Group continues address verification. If address was verified through all sources or the fact that the address is correct is confirmed by new source non response could be explained by reluctance or impossibility to participate in Project. Such subjects comprises a separate file for further examination by mobile team.

## **5. EXAMINATION PROCEDURES, para 1**

**5.1** It is expected that subject will ordinarily arrive with his appointment card and self-interview form received by mail.

## **5.2 REGISTRATION AND INFORMED CONSENT, para 4**

Person responsible for this procedure is registrar.

After obtaining consent registrar will print out bar-code labels with subject's ID to label them to data collecting forms, then date and label Control Form and put them to subject's envelope. Data collecting forms as well as specimen labels are attached at corresponding examining station. At each examining station, the study personnel will remove a label from the subject's envelope, label and complete the study form, and return the form to the subject's envelope. Specimens labels and ID labels are used for Blood and Urine collection forms, as well as for specimen containers. Examiner at each station will record information indicating whether the particular exam component was completed in the Control Form. The Control Form and instructions for its use appear in Appendix B-5-4. After receiving the envelope, the subject will be directed or taken to the first examining station where interviewing takes place.

### **5.2.2. URINE COLLECTION AND POST-COLLECTION PTOCEDURES AT THE EXAMINING CENTER**

Para 2, starting from the second line.

Personnel assisting with the urine collection procedure will use the next available row of specimen labels and affix the first label on the specimen collection form along side the subject's ID label (which will be obtained from the subject's envelope). The remaining specimen ID labels of the same row will be attached first to the larger urine collection tube, then to the aliquotted specimen tubes. This procedure will establish the link between the subject's ID and the specimen ID (see Section 3.3).

#### **5.2.2.2 EQUIPMENT AND SUPPLIES**

(changes are typed italic)

Supplies needed for the urine collection *in the Screening Center* include

**Item 3**

- *Urine collection, processing and result form*

**Item 4**

Supplies needed for urine processing *in mobile team* include:

**5.2.2.6 INSTRUCTIONS FOR STORAGE AND SHIPMENT OF URINE SAMPLES**

(changes are typed italic)

The urine aliquots will be placed into *racks* and stored *in freezer* until shipment to the Central Laboratory. *After freezing aliquots will be placed into a plastic pack.* Shipments to the Central Laboratory will be made on a weekly or monthly basis. For shipment the samples will be placed into a *bag-refrigerator*. *After arriving to Central Laboratory a person responsible for samples storage will complete Part 2 in each form (urine shipment to Central Laboratory) which contains the following information: date of delivery, state of samples, name of person delivered a sample.*

**5.2.2.7 DATA COLLECTION AND TRANSFER TO DCC**

(completely changed)

Information regarding urine collection and processing will be documented on the Urine Collection and Processing Form. The form will be pre-labeled with the subject ID number. After determining that the subject is eligible for the urine collection, the nurse assistant will affix a specimen ID label onto the form and fill in Part 1 concerning sample collection recording the polyvitamin and medical information, the date and time of collection any problems with the sample. Data of urine processing procedure will be recorded onto Part 2 of the same form. The nurse assistant will document the number of filled tubes and quantity of urine in each of them. The form and instructions for its completion is presented in Appendix A-5-3.

If a urine sample is not collected on a subject, this fact will be recorded on the Urine Collection and Processing Form.

The urine samples themselves will be shipped to the Central Laboratory accompanied by the Urine Collection, Processing and Result

The Central Laboratory itself will perform the control under the urine collection and shipment as well as trace the obtaining of the results. All the information from forms will be entered to the local computer DB in the Central Laboratory and sent to DCC on disks.

**5.2.5.4.1 COMPARISON WITH THYROID PALPATION, instead of ULTRASOUND****5.2.5.7 PROVIDING RESULTS TO THE STUDY PARTICIPANTS/EXIT PROCESS**

1-st para, 3-rd line

written copy of Summary of thyroid examination

1-st para, 10-th line

Original of Summary of thyroid examination will remain in the subjects envelope. The subject will also receive completed form of complex examination (adopted by the Ministry of Health) to be passed to home polyclinic. The physician will answer any questions and clarify any information that the subject or his parents find unclear. The subject will also be told that in case of abnormalities in blood he will be informed additionally by phone or mail.

**5.3 REPORTING RESULTS TO HOME POLYCLINIC**

After laboratory tests results are available, endocrinologist will fill in the Final Endocrinologic Summary and Recommendations. If some deviations will be found in blood test the information of this as well as new recommendations will be given to subject by phone or letter.

## **5.5.1 THYROID REFERRALS TO THE DESIGNATED ENDOCRINOLOGICAL FACILITY**

### **CLINICAL PRESENTATION/HISTORY**

3-rd line:

- diffusive goiter of 2-nd degree (only in combination with other criteria) and more.

### **8.1.1 DIAGNOSTIC CATEGORIES**

#### **8.1.1.1 THYROID CATEGORIES** (According to ICD 9 Code)

Nodular goiter non-toxic 241

Excluded: thyroid adenoma (226), cyst adenoma (226)

Thyroid cyst 246.2

Excluded: cyst adenoma (226)

*(Quality Control Group)*

While working with forms we paid attention to formalization of entered data, and availability of information allowing to trace effectively subjects and perform quality control.

Particular attention was paid to formalization of diagnosis text. Clinical Group of the Project suggests that while analyzing cases of diseases depending on thyroid dose one should consider specificity of clinical course of thyroid pathology in patients with different dose loads. To perform such analysis diagnoses recorded to Preliminary and Final Medical Summary, as well as to Hospitalization, Endocrinological, and Surgical Forms should be formalized and compatible in details. Below is given our point of view to this question.

While formulating clinical diagnosis aside with nosological form having individual ICD code usually a series of clarifying parameters are used. Some of them are unique and describes only specific nosological forms, for example, TNM - is thyroid cancer, hypertrophied type, false nodular variant - chronic lymphocital thyroiditis. Others are universal, for example: level of thyroid increase, thyroid functional state. Thus, clinical diagnosis is formed from unique and universal parameters located in strict sequence. This sequence is regulated for endocrinologist by Pattern for formulating clinical diagnosis (Scheme 1), and for program engineer and data entry operator - by algorithm and reference envisaged for each diagnosis.

Pattern is suggested for use in all the forms containing text formulation of diagnosis: Preliminary and Final Medical Summary, Hospitalization Form, Endocrinological and Surgical.

We think that such approach on the one hand will allow to formalize diagnosis without creation additional codes, and on the other hand - will allow to keep unique text diagnosis and analyze evolution of not only nosological form but also each separate symptom at different steps of examination and time.

Main diagnosis of thyroid pathology :IDC-9 | | | | , | |  
 Nosology: | | | | | | | | | | | | | | | | | | | | | |  
 (Suspicion | | | | | | | | | | :IDC-9 | | | | , | | | )  
 Type, variant | | | | | | | | | | | | | | | | | | | | | |  
 Degree of thyroid: | | | Function: | | | | | | | | | | | | | | | | | |  
 Nodule/tumor location: right lobe ☐ , left lobe ☐ , thymus ☐  
 Nodule specificity: | | | | | | | | | | | | | | | | T | | | N | | | M | | |  
 (according to USE ☐ , cytology ☐ , morphology ☐ )  
 Surgery: No , ☐ , because of main disease ☐ ,  
 other disease: | | | | | | | | | | | | | | | | :IDC-9 | | | | , | | |  
 Nodule/tumor location: right lobe ☐ , left lobe ☐ , thymus ☐  
 Totally | | | times, Date: 1) . | | | | | | | | | | 2) . | | | | | | | | | |  
 Surgery: TTE ☐ , STTE ☐ , HTE ☐ ,  
 other | | | | | | | | | | | | | | | | | | | | | |  
 Post-surgical treatment: No ☐ , if Yes ☐ , note  
 Gamma therapy: Dose | | | | | | | | | | | | Date | | | | | | | | | |  
 Radioiodine therapy: Dose | | | | | | | | | | | | | | Date | | | | | | | | | |  
 Complications after surgery: No ☐ , if Yes ☐ , note:  
 | | | | | | | | | | | | | | | | :IDC-9 | | | | , | | |  
 Disease progress:  
 (nodule growth ☐ , new nodule ☐ , metastases ☐ )  
 No ☐ , if Yes ☐ , note location  
 | | | | | | | | | | | | | | | | | | | | | |  
 Combination with other thyroid pathology  
 | | | | | | | | | | | | | | | | :IDC-9 | | | | , | | |

### Scheme1. Pattern, formulating of clinical diagnosis

Because at the screening stage disagreements appear regarding criteria “normal thyroid” we suggest the following. Conclusion is made to euthyroidal subjects with 0 or 1A degree of thyroid according to palpation data, when there is no changes or minor changes in thyroid according to ultrasound examination noting ultrasound size of thyroid. Examples: 1).Normal thyroid 0 degree. (100%) euthyroiditis.2).Normal thyroid 1A degree. (130%) Minor thyroid ultrasound changes euthyroiditis.

Taking into consideration that the majority of cohort subjects do not have changes in thyroid, a simplified variant of Pattern could be applied to them (Scheme 2).

**Conclusion:** if normal thyroid ☐, note  
degree of thyroid : 0 ☐ or 1a ☐, thyroid ultrasound size |\_|\_|\_|%  
Minor ultrasound changes: Yes ☐ No ☐ Function: Euthyroiditis

**Scheme 2. Pattern, conclusion for cohort subjects with normal thyroid**

While coding diagnosis “Suspicion to\_\_\_\_\_”, we suggest to use traditional IDC to which in atypical state figure 7 is added, i.e. if thyroid cancer code - 192.0, so suspicion to thyroid cancer - 192.07.

It should be noted that in the course of work we faced with difficulties in tracing subjects who referred from endocrinological department to National Center of Thyroid Oncopathology, do not come to hospitalization, or refuse from surgical treatment. It is also

difficult to find the results of thyroid FNB performed at hospitalization stage by physician who does not work in the Project. This information is not envisaged by the forms, and so it comes to Screening Center and DCC not in time. That is why we suggest the following changes:

1). Hospitalization Form (Endocrinological):

FNB - No ☐, if Yes ☐, Date

Recommendations:

Referred to NCTOP - No ☐, if Yes ☐ Date of hospitalization

2). Hospitalization Form (Surgical):

Surgery Yes ☐, if No ☐, note the reason:

patient refusal  
no need in surgery

FNB No ☐, if Yes ☐, Date

Recommendations:

Form Individual Medical Interview. Item 3, the question concerns diseases not connected with thyroid

Pathomorphological Form has been reviewed.

Variants of forms for joint discussion are presented at Appendixes 1, 2, 3,4

**(Data Coordinating Center)**

For the reported period Section 9 "Data management" is in the process of review and updating in accordance with current procedures.

**Milestone 14: Development of instructions for filling in and data entry of epidemiological, screening, laboratory, and hospitalization forms.**

In the 4-th quarter 1998r. DCC completed instructions for filling in and data entry of epidemiological, screening, laboratory and hospitalization forms. The list of forms, instructions and corresponding annexes to Operational Manual is presented in Table 6.

**Table 6**

**List of instructions for forms completion and data entry.**

Nº	Form	Instruction how to complete	Instruction for data entry	Annex in OM
	<b>APPENDIX A DATA COLLECTION FORMS AND SPECIFICATIONS</b>			
1	Initial Abstract Form	+	+	A-3-1
2	Contact Form	+	+	A-3-2
3	Initial Interview Form	+	+	A-5-1
4	Annual Interview Form	-	-	
5	Mother's interview (at the period of breast feeding)	-	-	A-5-2
6	Urine Collection, Processing and Results Form	+	+	A-5-3
7	Blood Collection and Processing Form	+	+	A-5-4

8	Ultrasound Examination Form	+	+	A-5-5
9	Thyroid Palpation Form	+	+	A-5-6
10	Medical Interview Form	+	+	A-5-7
11	Needle Biopsy Form	-	-	A-5-8
12	Adverse Event Report	+	-	A-5-9
13	Blood Tests Results Form	-	+	A-6-1
14	Summary Of Medical Screening and Recommendations	+	+	A-7-1
15	Pathomorphological examination Form	-	-	A-8-1
16	Hospitalization Abstract Form	+	+	A-8-2
17	Death Data Form	+	-	A-8-3
<b>APPENDIX B</b>				
<b>MANAGEMENT FORMS AND REPORTS</b>				
18	Locator Form	-	+	B-5-2
20	Control Form	-	+	B-5-4
21	Transmittal Forms	-	-	B-5-5
22	Nonresponse Form	-	-	B-9-1

### **Milestone 15: Development of Quality Assurance Manual**

*(Quality Control Group, DCC)*

In the 4-th quarter activity aimed at review of materials and improvement of Quality Assurance Manual was continued. General part of the Manual is presented in Appendix 5.

In the framework of quality control a process was initiated for development of algorithm for revealing of missing forms, diagnosis deviations on different stages regarding thyroid nodules according to ultrasound examination and pathomorphological examination.

Algorithm for revealing missing Hospitalization and Pathomorphological Forms is shown on Fig.2. Implementation of given algorithm is impossible now because of lack of data regarding subject transfer from Endocrinological Department to Oncological Department in Hospitalization Form, and lack of agreed Pathomorphological Form.

Algorithm for revealing disagreement in the main diagnosis is shown on Fig.3. Algorithm is based on comparison of ICD coded diagnoses from clinical and Patomorphological forms. Implementation of given algorithm is impossible at present because of above mentioned reasons.

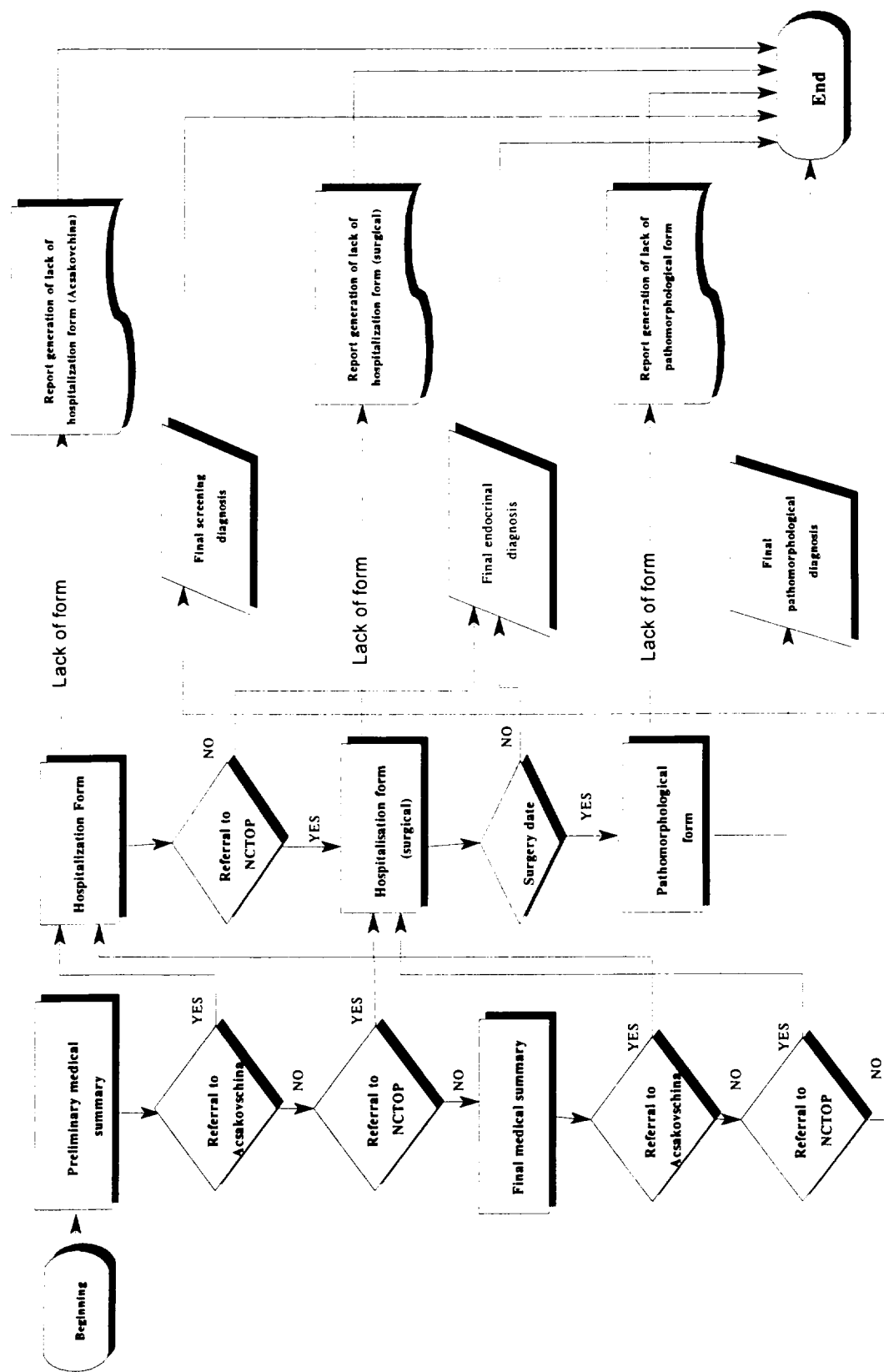
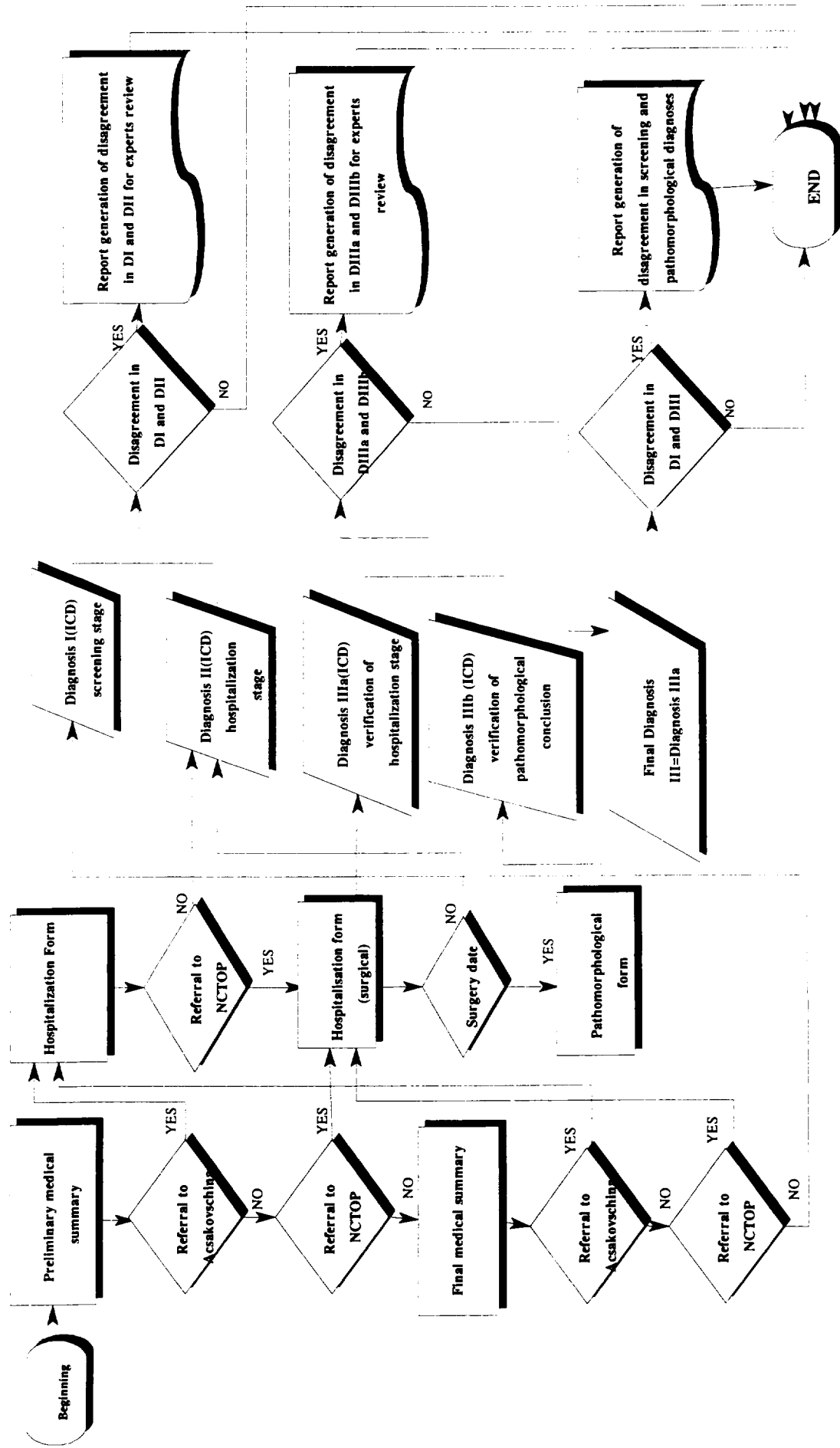
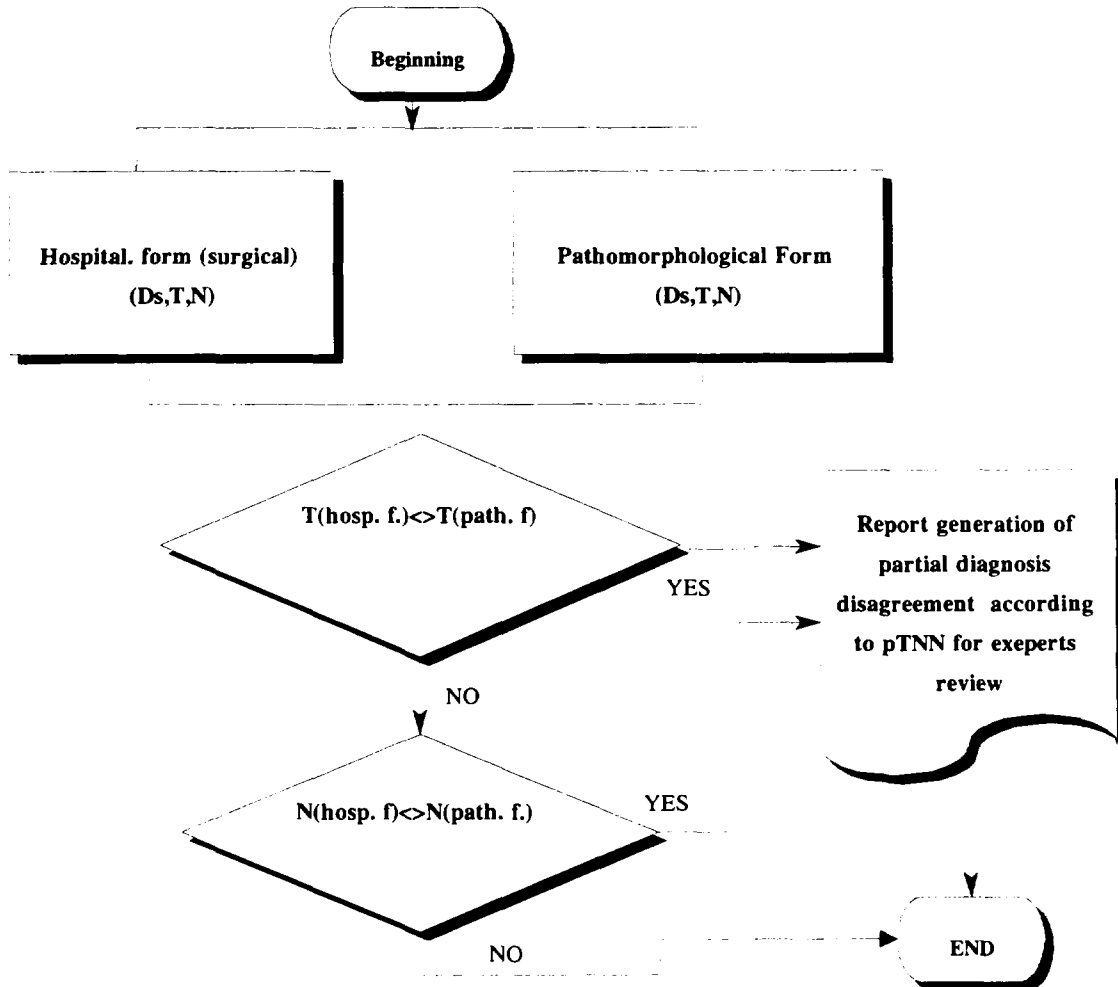


Fig 2. Algorithm for revealing of missing clinical forms (Hospitalization (Acasakovschina), Hospitalization surgical, Pathomorphological)



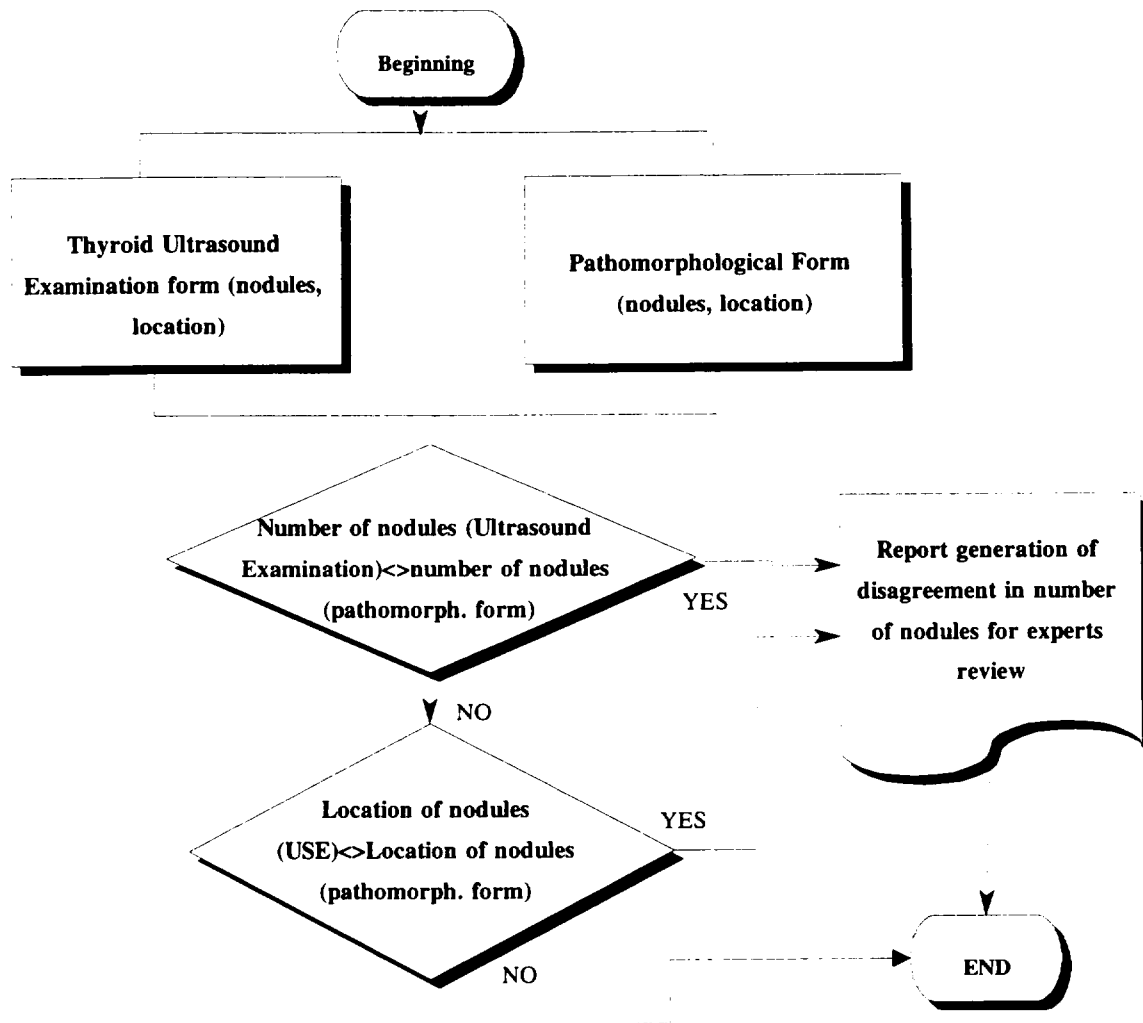
**Fig 3. Algorithm for revealing of disagreements in the principal diagnosis**

Algorithm for revealing of partial disagreement in diagnoses according to pTNM is presented in Fig.4. For its implementation it is necessary to make some changes to diagnosis formulation. pTNM categories should be distributed in DB to fields.



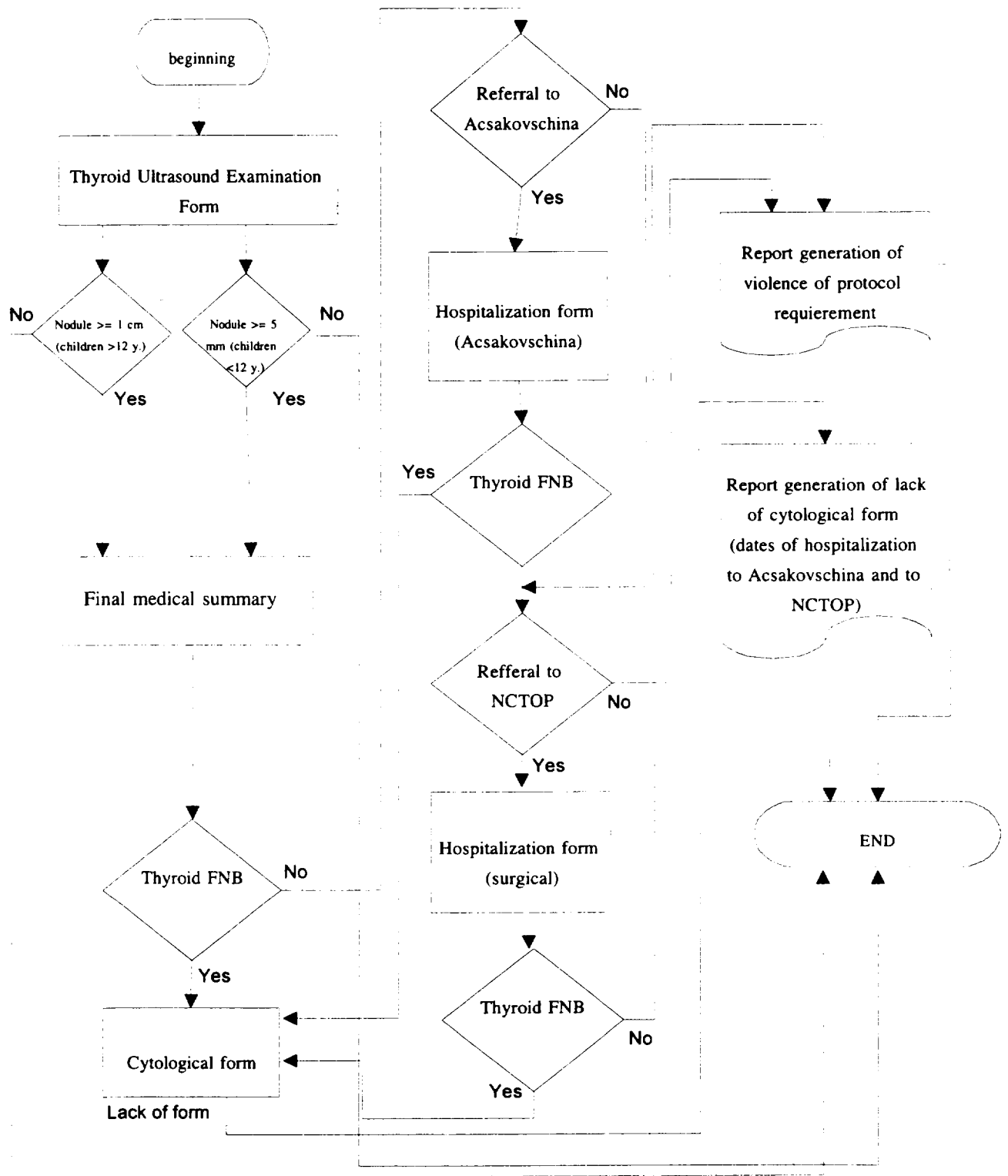
**Fig. 4. Revealing of partial disagreement in diagnosis according to pTNM**

Algorithm for revealing of partial disagreement in diagnose according to the number of revealed nodules is presented in Fig.5.



**Fig. 5. Revealing of partial disagreement in diagnose according to the number of revealed nodules**

Algorithm for control under the procedure of thyroid FNB in accordance with the requirements of the Protocol, and revealing of missing forms of cytological examination is presented in Fig.6. Implementation of given algorithm will be possible following acceptance of Cytological Form and making changes to DB.



**Fig. 6. Algorithm for control under the procedure of referral to thyroid FNB in accordance with the requirements of the Protocol, and revealing of missing forms of cytological examination**

Thus, to automatize procedures of quality control it is necessary to make urgent changes to forms and DB structure as well as to data entry programs. Otherwise we will continue to accumulate information that is impossible to claim for analysis.

**Task № 6. Data management.**

**Milestone16: Design of part of data entry software for epidemiological, screening and hospitalization information.**

*(Data Coordination Center)*

For the reported period DCC has performed the following activities :

- development of software for data entry of Death Form, its experimental running
- experimental running of software for data entry of Pathomorphological Form
- experimental running of software for data entry of FNB and Cytology Form
- modernization of software for data entry of Summary of Medical Screening and Recommendations and Hospitalization Form;
- modernization of software for data transfer from Screening Center and Central Laboratory to DCC.

Experimental running of software for data entry of FNB and Cytology Form as well as Form of Pathomorphological examination showed the necessity of making changes to the structure of above mentioned forms.

**Milestone 17: Data entry of epidemiological, screening, laboratory, and hospitalization forms.**

Data entry by Project Units in the 4-th quarter is presented in Table 7

**Table 7**

**Data entry by Project Units**

N	Forms	Project Units
1	Initial Abstract Form	Epi Group(DCC local network)
2	Contact Form	Epi Group(DCC local network)
3	Death Form	Epi Group(DCC local network)
4	Initial Interview Form	Dosimetry Group(DCC local net.)
5	Urine Collection, Processing and Results Form	Central Laboratory
6	Blood Collection and Processing Form	Central Laboratory
7	Blood Tests Results Form	Central Laboratory
8	Locator Form	Screening Center
9	Control Form	Screening Center
10	Ultrasound Examination Form	Screening Center
11	Thyroid Palpation Form	Screening Center
12	Medical Interview Form	Screening Center
13	Summary Of Medical Screening and Recommendations	Screening Center
14	Hospitalization Abstract Form	DCC (local network)

15	Pathomorphological examination Form	DCC (local network)
16	Fine Needle Biopsy Form	DCC (local network)
17	MOD registration log	DCC (local network)

Presented in Fig.7 information is evidenced that data entry at the stage of screening is performed satisfactory.

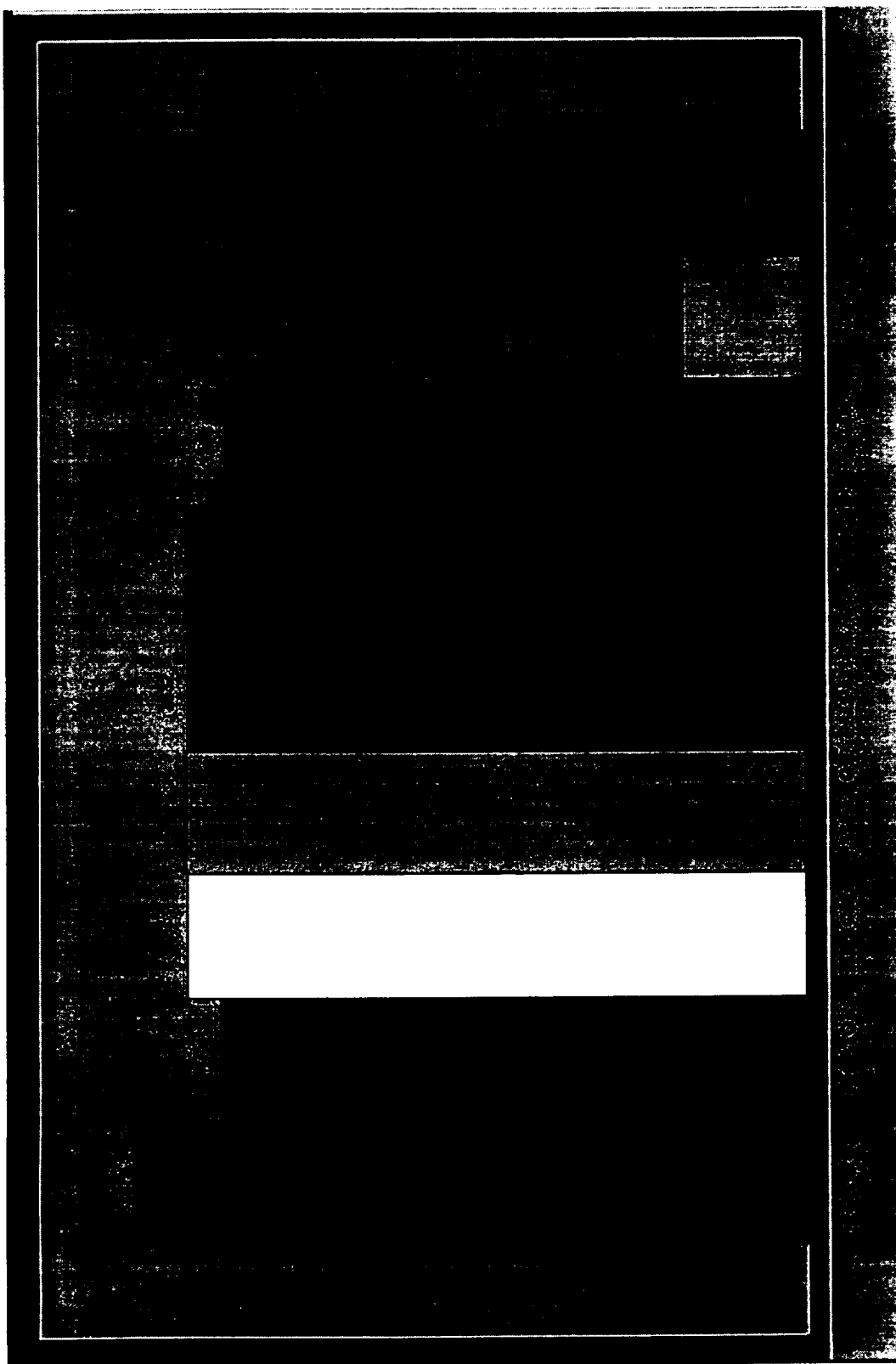


Fig. 7. Distribution of entered to DB screening and hospitalization forms

**Milestone 18: Transfer to the DCC file server of the data, entered in local computers of the screening center and central laboratory, and quality control of these data.**

*(Data Coordinating Center)*

For the reported period DCC personnel transferred data from Project Units to DCC server. Data came to DCC on disks periodically once a week. For given activity specially developed software was used. At the same time a check have been performed for data type and range. Numericals and numerical-letter codes have been also checked for possibility and range.

Software is designed so that it selects newly entered records and does not touch records entered by the moment of ordinary data transfer. While adding data to server check is performed for presence of this record. If record is absent it is directly added, and if it is presented on server updating of record is made

**Milestone 19: Design of part of the query software for the epidemiological, screening and hospitalization information.**

*(Data Coordinating Center)*

For the reported period DCC has completed query subsystem for Epi Group. Example of the report generated by query subsystem on the base of the results of its activity according to chosen criteria is presented in Fig. 8.

DCC started designing report of screening examination, hospitalization, pathologies, number of made diagnoses, examined subjects for period of time and in accordance with sex.

Unfortunately, data received as a result of some queries reflects actual situation not adequately enough. This situation could be explained by insufficient formalization of forms in sections of making diagnosis, initially revealed disease or repeatedly, disease was revealed in the Project or out of Project, etc.

In the 4-th quarter DCC started designing DB of personnel. This DB will contain family names and names of all the staff involved in the Project. Besides, it will contain phone numbers, position, place of work, date of coming to Project and date of quitting, Project Unit. Each member of the Project will have personal ID number which will be noted in informational documents. DB will contain information of personnel certification, and also some additional information of personal data of Project employee.

## Первичные визиты

За период времени: 01.10.98 - 31.12.98

Из них, при условии :

Пол:	Без ограничения	Год рождения:	Без ограничения
Область:	Без ограничения	Район:	Без ограничения

Произошло следующее распределение статусов :

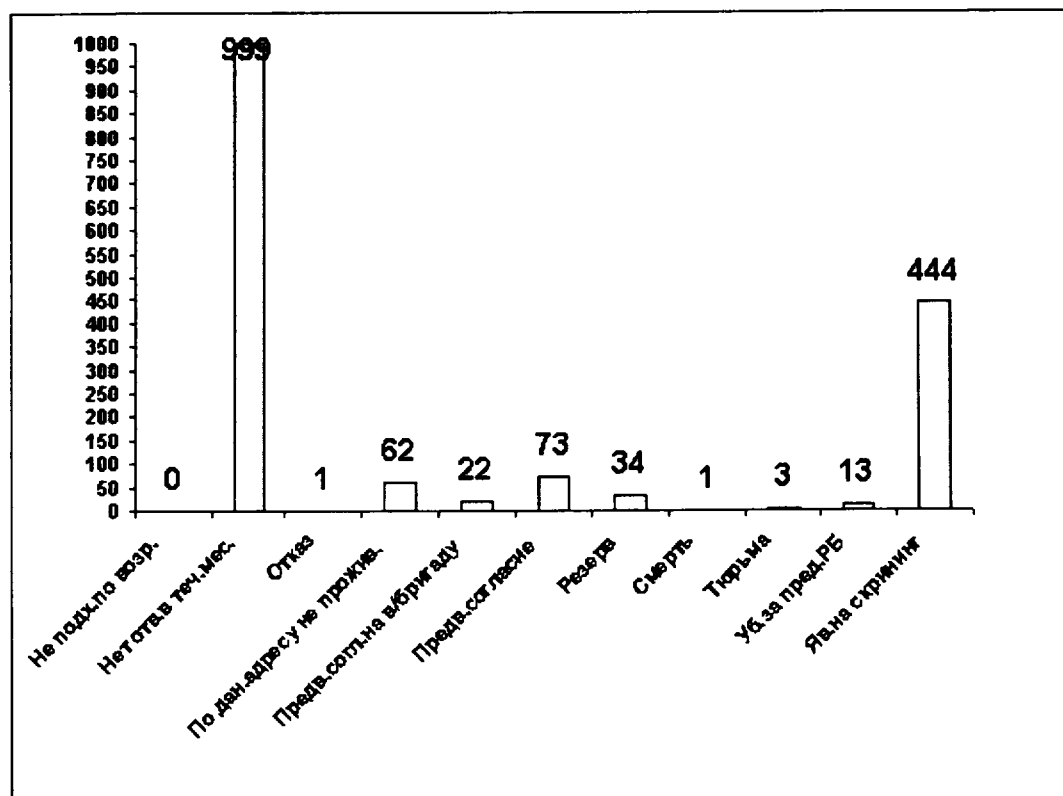
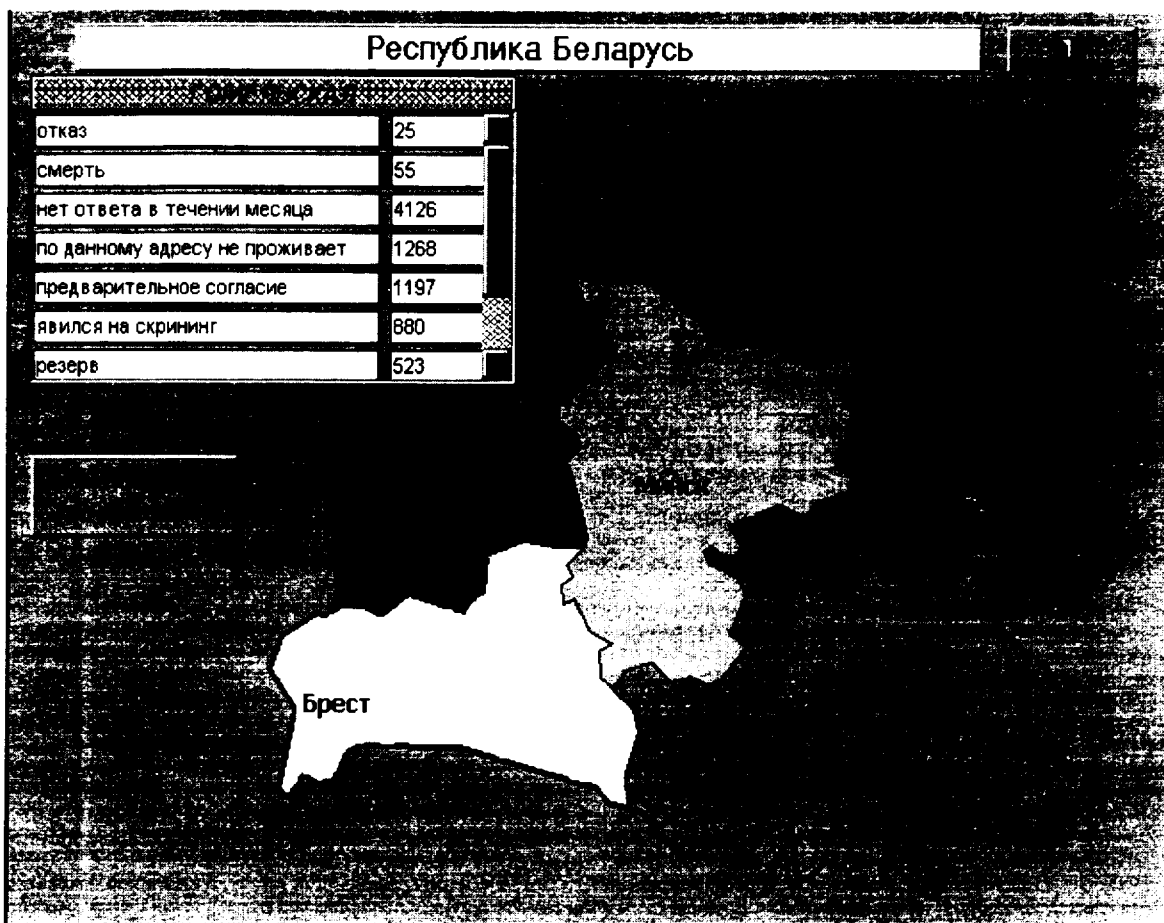


Fig.8 Example of report generated by query subsystem



**Fig. 9 Screen for estimation cohort state depending on the place of residence.**

For the repeated period a software has been developed that allows to estimate this or that indices of cohort state depending on the place of residence. Thus, one could see on the map of the Republic dynamical changes in cohort state, for example, epidemiological statuses (Fig.9). Furthermore this software will be used for estimation of disease distribution and other clinical indices, revealed in the process of subjects examination.

**Milestone 20: Analysis of the results and preparation some progress report on the cohort selection, scheduling of screening exams, subject flow through exams and data entry.**

*(Data Coordinating Center).*

*(Epi Group)*

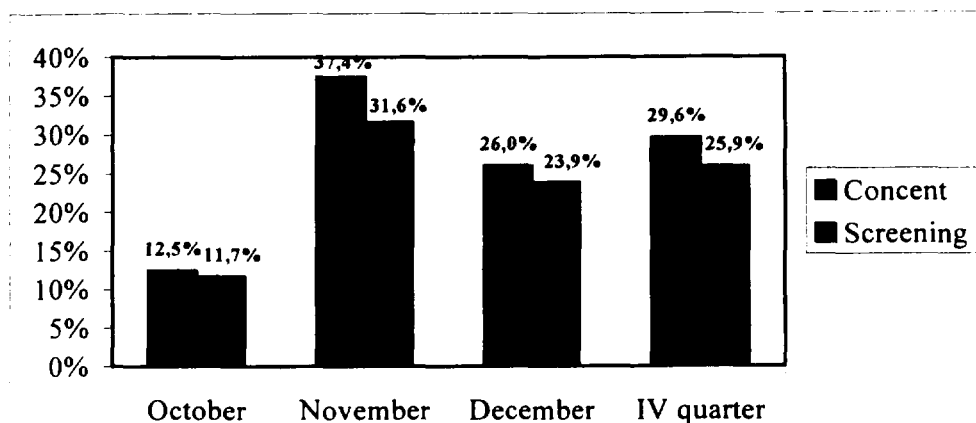
In the 4-th quarter 1608 individuals have been invited to initial visit. On the results of analysis of cohort state by the end of the quarter the following distribution of statuses occurred (Table 8).

**Table 8**

**Distribution of statuses among invited to initial visit in the 4-th quarter**

Status	Number of Subjects			
	October	November	December	total
No response within a month	194	466	368	1028
does not reside given address	4	16	34	54
Preliminary consent	31	302	3	336
Refuse	0	1	0	1
Death	0	0	0	0
Moved out of Belarus	0	1	3	4
Reserve	12	20	7	39
Does not fit by age	0	0	0	0
Preliminary consent to be examined by mobile team	2	1	143	146
Imprisoned	0	0	0	0
<b>Total</b>	<b>243</b>	<b>807</b>	<b>558</b>	<b>1608</b>

Thus, from the total number of invited for 4-th quarter 418 inds, have passed screening examination. 49 subjects came to initial screening with previously received invitations (agreed or voluntary shift of visit data). Totally, 467 subjects have passed initial screening in the 4-th quarter. Percentage of received consents to examination in the 4-th quarter is at average 29,6%, percentage of those who passed examination to those who was invited is -25,9 (Fig. 10). The majority of consents as well as visits to examination in compare to invitations was observed in November. This fact could be explained by use of address files from Address Office of Mink and Mink Blast in November.



**Fig. 10. Dynamics of indices of number of patients who gave consent to initial examination and undergone screening from the total number of invited**

Fig. 11 shows distribution of preliminary consents given by cohort subjects to screening examination for the 4-th quarter day by day.

Fig 12 shows distribution of initial visits to screening for the whole period of Project activity by months.

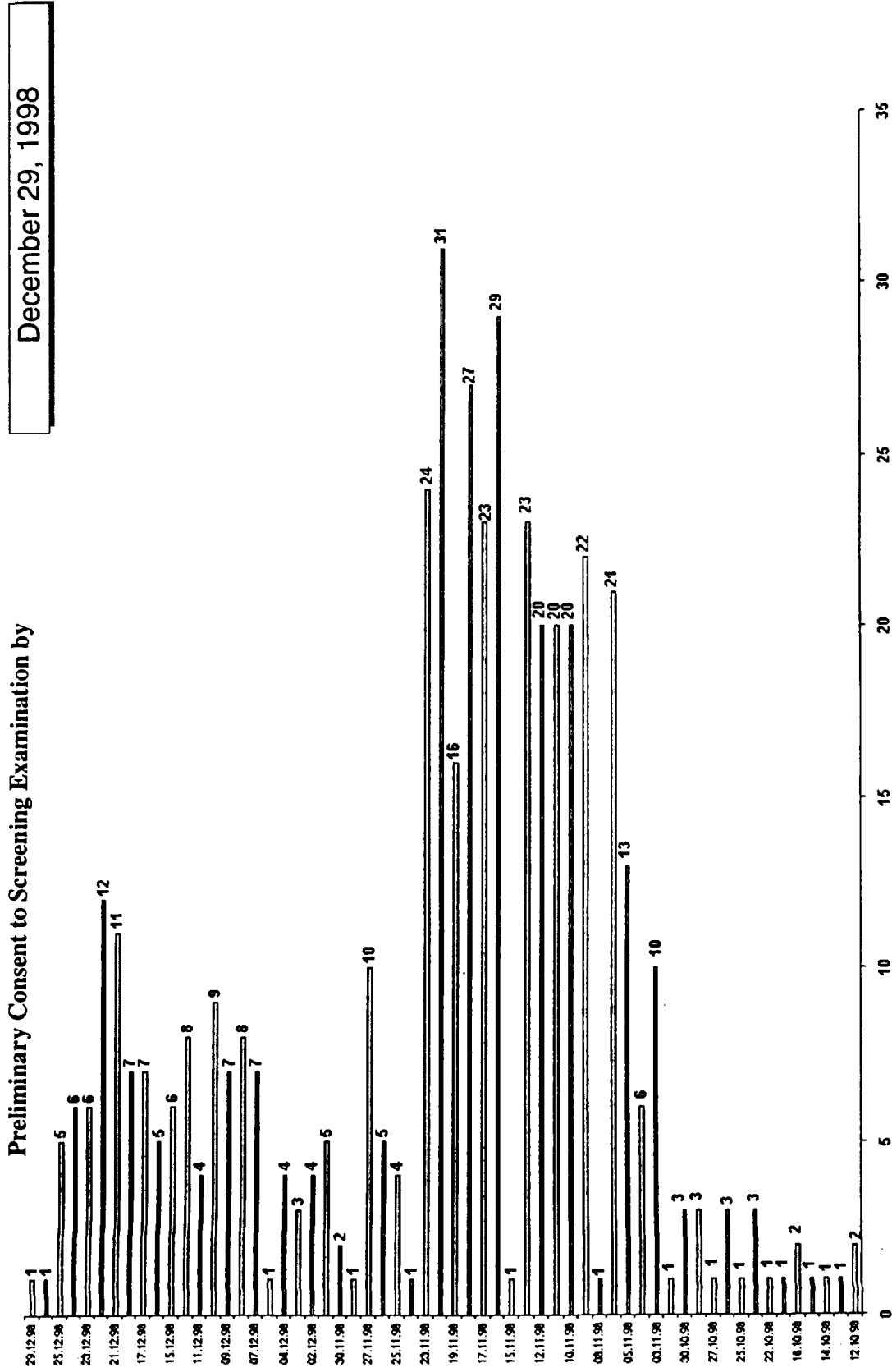


Fig.11 Distribution of preliminary consents to screening for reported period

Fig.11 Distribution of preliminary consents to screening for reported period

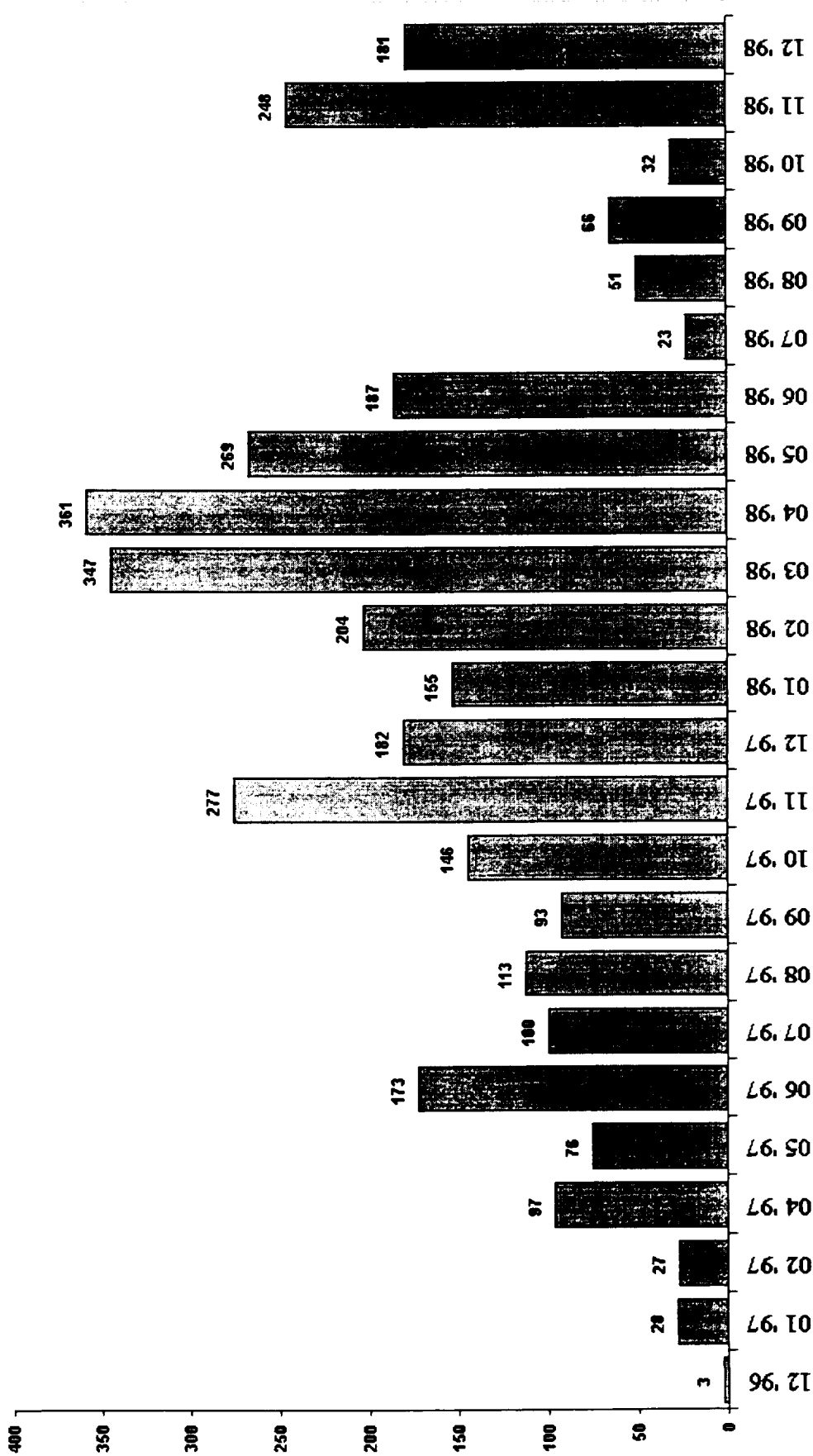
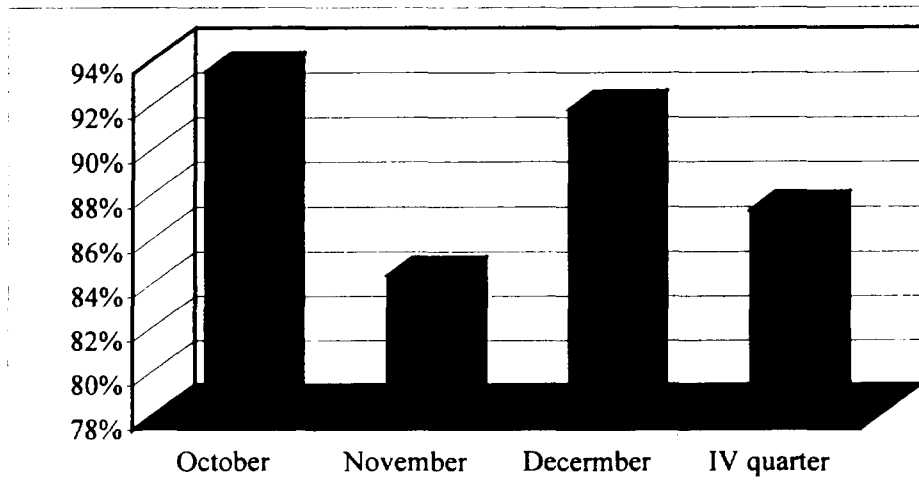


Fig. 12 Distribution of initial visits to screening for the whole period of Project activity

Percentage rate of number of subjects undergone examination to those given consent at average for the quarter is 87,3%, varying from 84,4% in November to 93,5% in October (Fig. 13).



**Fig. 13. Dynamic of indices of number of subjects undergone initial screening examination from the total number of those given consent**

In the 4-th quarter subjects were invited to repeated visit.

443 invitations have been sent. Statuses of cohort subjects are distributed the following way (table. 8).

**Table 8**

**Distribution of statuses among subjects invited to repeated visit in the 4-th quarter**

Status	Number of Subjects
No response within a month	275
Does not reside given address	2
Preliminary consent	146
Refuse	1
Death	0
Moved out of Belarus	0
Reserve	18
Preliminary consent to be examined by mobile team	1
Imprisoned	0
<b>total</b>	<b>443</b>

Fig 14 presents distribution of repeated visits for the whole period of Project activity.

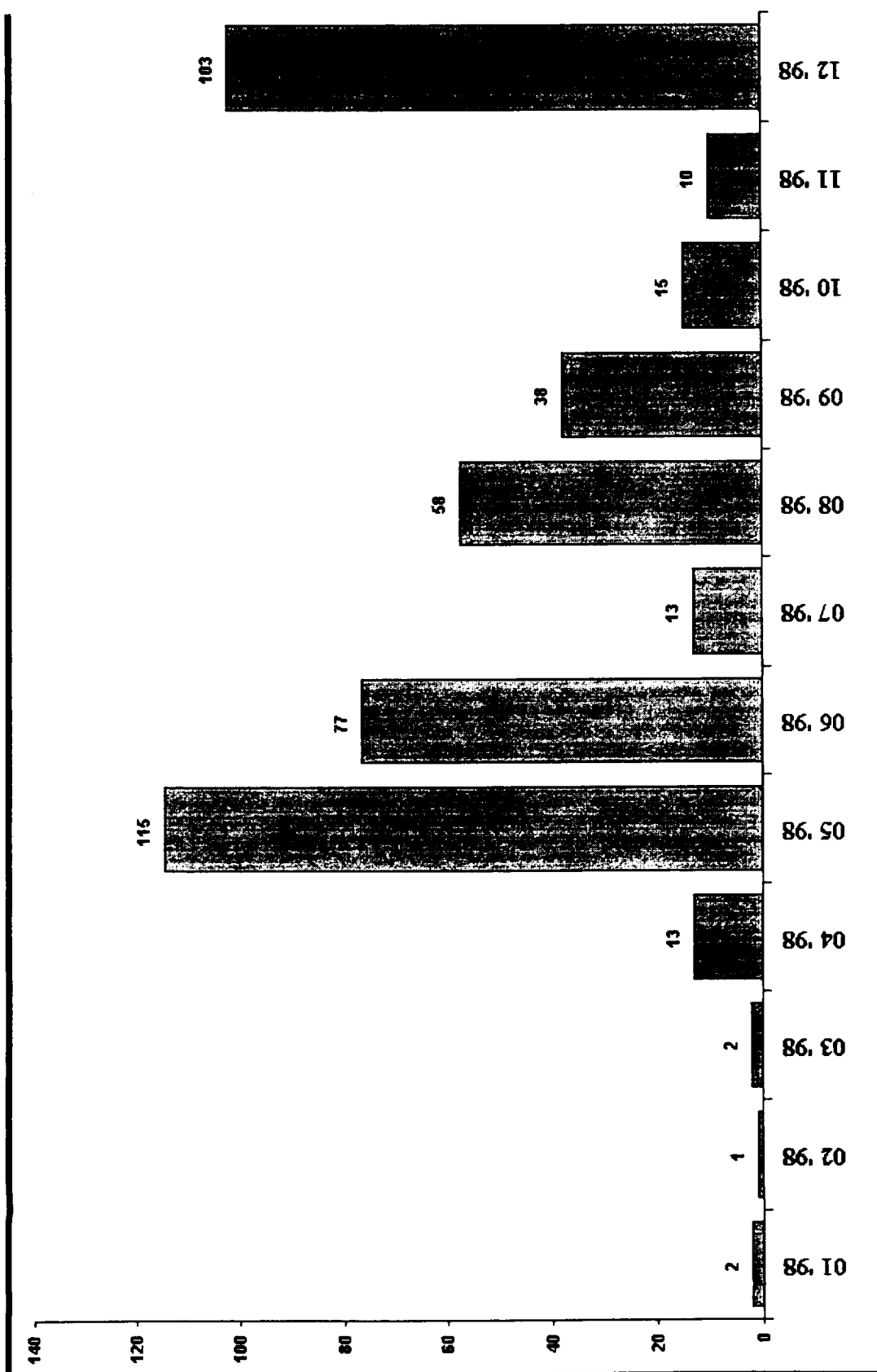
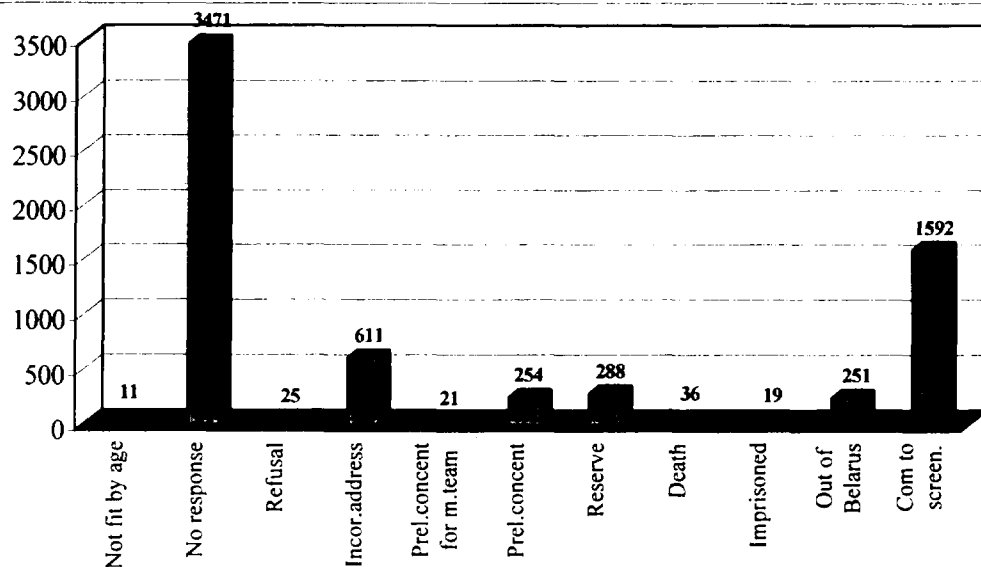


Fig. 14 Distribution of repeated visits to screening for the whole period of Project activity

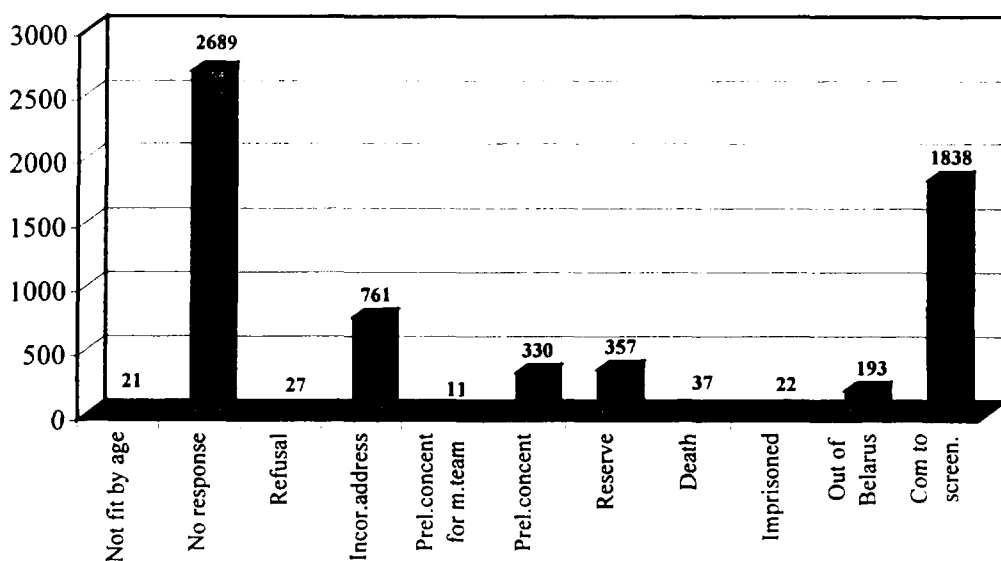
Thus in the 4-th quarter 33% of invited subjects agreed to come to repeated examination, 62% from agreed subjects came to examination. Besides, 34 subjects came to repeated visit in accordance with invitations received before 1.10.98. Totally, 125 subjects have undergone repeated examination in the 4-th quarter.

Totally, for the period of screening activity 4.330 subjects have undergone initial examination (1.592 subjects from high dose group, and 1.838 - from low and middle dose groups).

Figs. 15 and 16 present current features of cohort state for the whole period



**Fig. 15. Distribution of statuses of high dose group subjects undergone examination from 21.12.96 to 31.12.98.**



**Fig. 16. Distribution of statuses of low and mid dose group subjects undergone examination from 21.12.96 to 31.12.98.**

Results of searching activity for the whole period of Project operation are presented in Table 9.

**Table 9**

**Results of searching activity for the period of 21.12.96 - 31.12.98 r., %**

Searching outcomes	Group		Total
	High dose	Mid and low dose	
Subject address is defined	78,0	71,4	74,6
Subject address is not defined	22,0	28,6	25,4

Using different sources of address search it was managed to find addresses of 74,6% of cohort subjects. While contacting with cohort subject through found address the following results have been obtained (Table 10.)

**Table 10**

**Results of contacts with cohort subjects through found address, %**

Contacts outcomes	Group		total
	High dose	Mid and low dose	
response	37,9	45,1	41,4
no response	52,8	42,1	47,9
wrong address	9,3	12,1	10,7

41,4% of subjects whose addresses have been defined responded to invitation. At the same time response (contact outcome) was both positive (consent to screening in the Dispensary of Radiation Medicine or by mobile team), and negative (subject does not fit by age, imprisoned, moved out of Belarus) following which has been excluded from the cohort. High percentage of contacts is characterized by the result "no response" At the same time obtained experience of work with subjects through their places of residence (visit subjects places at Khojniki and Bragin), analysis of their coming to mobile team examination, twice confirmed through some sources subjects addresses allowed to make a conclusion that the majority of subjects not responded to invitation do reside defined address but do not have a possibility or wish to come to Minsk to examination.

Efficiency of subjects search for the past period agrees with those during pilot stage of project (search of 600 addresses) and is rather high.

Fig. 17 presents distribution of "no response" group by the rajons of Gomel Oblast. From this figure it is evident that the most perspective rajons for mobile team are Khojniki, Bragin, Retchitsa and Vetka rajons.

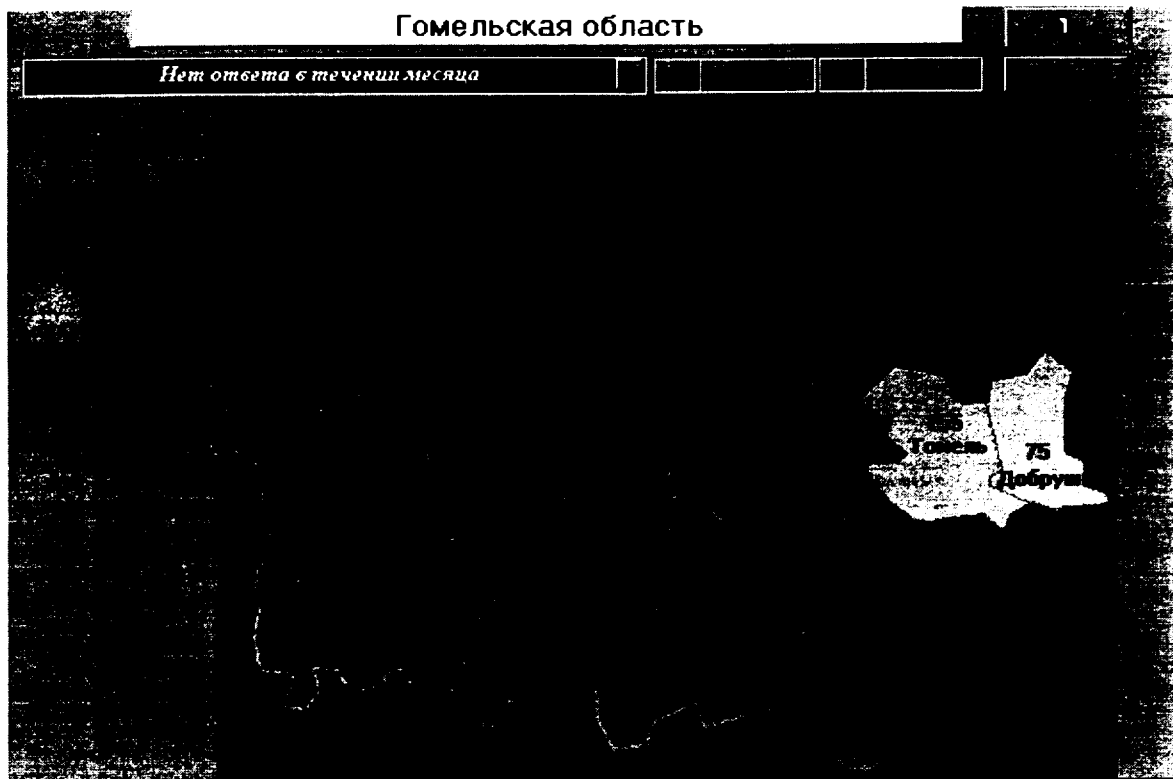


Fig.17 Distribution of "no respondents" by the rajons of Gomel Oblast

Fig.18 presents the number of deaths by the rajons of Gomel Oblast

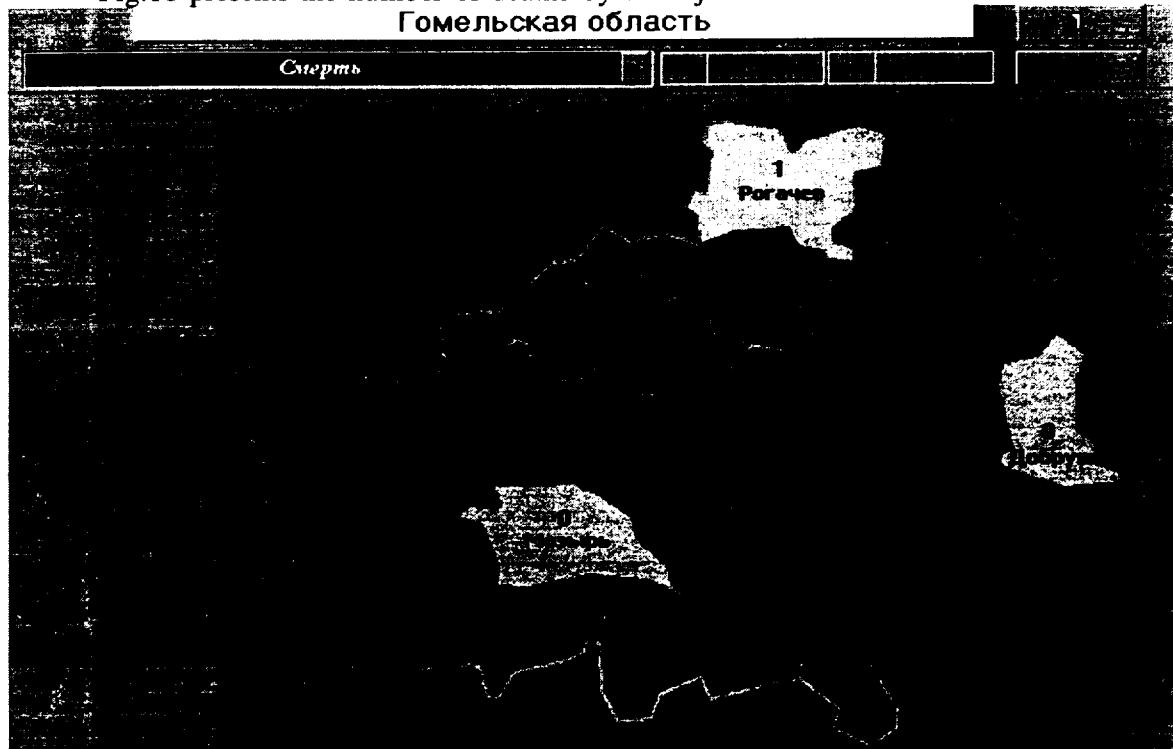


Fig. 18 Distribution of deaths cases by the rajons of Gomel Oblast

Review of presented data allows to select the following perspectives of cohort selection.

- Examination by mobile team at the places of residence of subjects with defined addresses, who do not response to invitation and comprise "reserve" group,
- Search through Address Offices subjects with undefined addresses;
- Increase subjects motivation to participate in Project

**Review of cases of thyroid cancer revealed in the course of BelAm study.**

*(Quality Control Group)*  
*(Screening Center)*

As a result of screening examination of 3.435 cohort subjects for the whole period of Project activity 41 (1.2%) cases of thyroid cancer have been revealed.

Review of the structure of thyroid cancer patients showed that:

- in 13 ( 31.7%) subjects the diagnosis was made for the first time, at the same time in 2 of them (4.9%) - during repeated examination,
- rate female to male was 1.7:1,
- the majority of cases was revealed in 1998 r. - 12 subjects.

(Diagram 1.)(the 2-nd year of screening, 12 years following the accident), among the patients subjects under 6 y.o. at the time of the accident prevailed - 27 inds. (65.9%) (Diagram 2.),

- most of cases was diagnosed in children aged 11-14 y.o., i.e. in the period of puberty (15 subjects., 36.6%) (Diagram 3.),
- total number of subjects to whom diagnosis was made in childhood (under 17 y.o.) was 28 inds (68.3%). This figure more than twice exceeded number of adult patients (Diagram3)

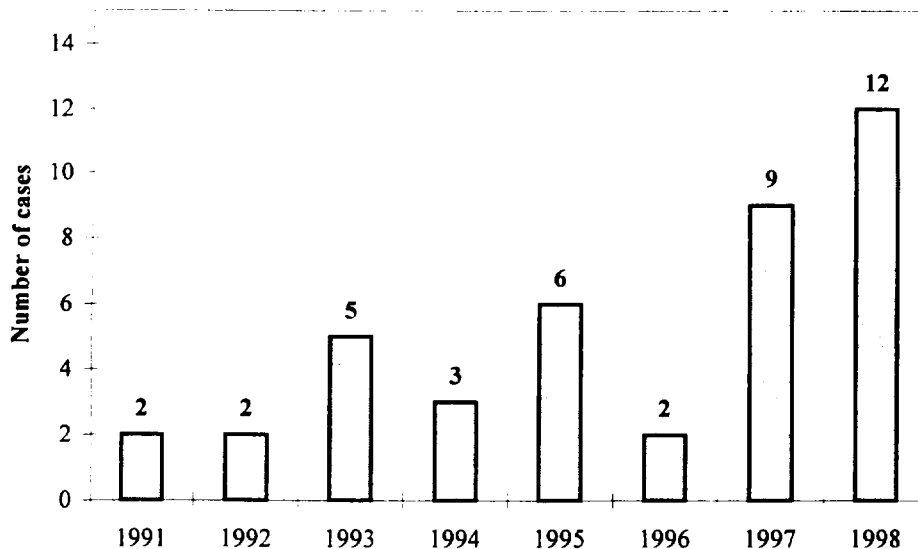


Diagram 1. Distribution of thyroid cancer cases depending on the year of surgery

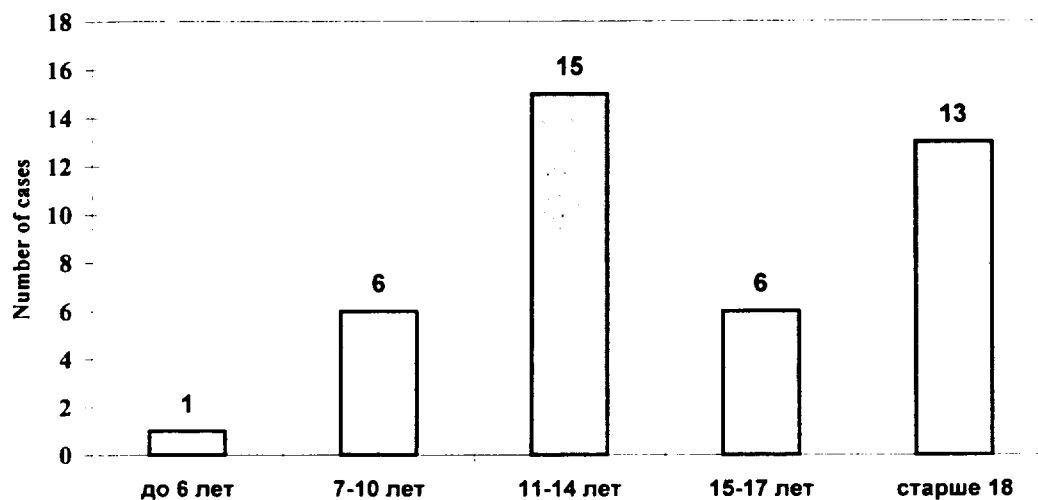


Diagram 3. Distribution of thyroid cancer cases depending on the age at the time of diagnostics

Preliminary review of thyroid cancer cases allows to mention the following:

- increase in number of thyroid cancers in 1997 and 1998 was happened at the cost of individuals aged 9 and more y.o. at the time of the accident
- one of the reasons of increase in number of thyroid cancers in the recent two years is a procedure of thyroid ultrasound screening that allows to reveal thyroid cancer at T 1-2.

It should be noted that all statements are of suppositional character and need to be verified and checked while enriching materials.

#### ***(Dosimetry Group)***

For the period of 1997-1998 Dosimetry Group has performed the following activity:

1. For 100 cohort subjects thyroid doses have been calculated
2. Initial dosimetric interview has been performed for 3.453 cohort subjects.
3. Repeated dosimetric interview has been performed for 433 cohort subjects
4. 2.760 dosimetric forms have been entered to dosimetric DB.

**Milestone 21: Design of image processing procedures, and data base of thyroid images.**  
***(Data Coordinating Center)***

For the reported period software for images processing modernized.

To optimize the work of the program initial algorithm have been changed. As a result of this the program creates not 300.000 catalogues corresponding to this or that subject ID as it was previously but only catalogues creating in processing of specific MOD. This significantly decreases time of program work.

In the course of program testing it was found out that in catalogue created for specific ID could also exist images not corresponding to given ID. It could be explained by the fact that program reads out N EXAM (# of examination) from image file, and through this index finds corresponding ID in the table of MOD registration log. Because at the time of image recording to MOD ultrasonographer keys N EXAM manually so the errors could occur while keying. It means: to each new ID at the time of recording to MOD a new N EXAM should correspond, but this does not always obeyed. To trace the correspondence of image files to specific ID of catalogue created for this ID at present it is suggested to perform visual control. Furthermore to avoid such mistakes it is expected to create a program that will read out necessary information directly from image file through recognition of ID and family name of subject.

To convert files of TIFF format to files of JPG format LVIEW PRO program is used. Active period of this program is limited by 20 days because we do not possess licensed copy of this program. That is why we need to obtain necessary version of the program or to develop program for conversion TIFF files to JPG files that could take long period of time

**Task No.7 The Estimation of Individual Thyroid Doses for Members of the Cohort**  
**Milestone 22: Conduct personal interviews for all subjects screened in the Project.**  
***(Dosimetry Group)***

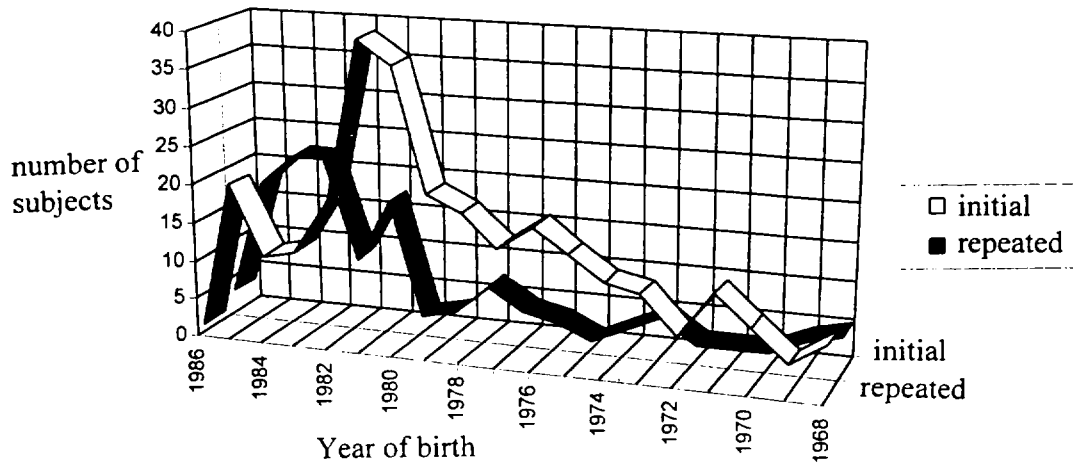
For the reported period (October 1 - December 30, 1998) 471 individuals were interviewed through individual dosimetric questioner (290 inds. - initial, 127 - repeated).

Review shows that the subjects come for examination

	initially	repeatedly
• on one's own	187	54
• together with mother	62	50
• together with father	17	14
• together with sister or brother	21	7
• with other accompanying	3	2

In the fourth quarter 7 questioners were completed for mothers in the period of breast feeding. 20 subjects came to interview without self-interview for Distribution of the cohort subjects is presented below

Age distribution of cohort subjects



Results of interviews with respect to the completeness of the subjects' answers is presented in Fig 22.1.

**Table 22.1.** Results of interviews with respect to the completeness of the subjects' answers.

Estimation of interview qual.	Initial interview	repeated interview
good	117	59
satisfactory	132	49
unsatisfactory	41	19

In the period of December 10 - 24, 1998 additional data collection through individual interviews was performed by the interviewer joined the mobile team in the town of Khoiniki.

Total number of cohort subjects come to examination was 174. 173 of them were interviewed (one subject refused from interview). 170 subjects were initially interviewed, and 3 - repeatedly)

Subjects come for examination

	initially	repeatedly
• on one's own	112	2
• together with mother	42	1
• together with father	4	-
• together with sister or brother	11	-
• with other accompanying	1	-

Distribution of 173 subjects' answers with respect to the quality of obtained data is shown in Table 22.2.

**Table 22.2.** Results of interviews with respect to the completeness of the subjects' answers.

Estimation of interview qual.	Initial interview	repeated interview
good	67	3
satisfactory	53	
unsatisfactory	50	-

**Table 22.3.** Total results interviews with respect to the completeness of the subjects' answers.

Estimation of interview qual.	Initial interview	repeated interview	total
good	184	62	246
satisfactory	185	49	234
unsatisfactory	91	19	110
TOTAL	460	130	590

Distribution of cohort subjects who had been interviewed in the reported period and in the period of 1996 to 1998 according to the dose intervals is presented in Table 22.4

**Table.22.4.**

Distribution of interviewed cohort subjects according to dose intervals.

Dose range, Gy	4-th quarter	1996-1998
< 0.3	206 (35%)	1036 (30%)
0.3-1.0	124 (21%)	809 (24%)
> 1.0	256 (44%)	1587 (46%)
Total	586 (100%)	3432 (100%)

**Milestone 23: Enter to the data base information from interviews collected in the course of the quarter as well as data from 1000 interviews that have been performed earlier; prepare the section of the Dosimetric Operations Manual related to data entry.**

Data entry of subjects' individual interview started in the third quarter was continued in the forth only for initially interviewed.

For the current quarter all initial interview data of the current quarter(460 forms) have been entered and 1000 interview forms of 1997.

Totally, from the beginning of the Project to December 30 1998 2.599

It was reviewed and updated an instruction for conducting of initial interview (Appendix 6) considering changes to interview form (Appendix 7) that have been proposed at the meeting of dosimetrists in Minsk (October 1998). An instruction have been prepared

(Appendix 8) describing the procedure of data entry software usage and operator activity while entering data of the initial interview to the data base.

**Milestone 24: Prepare software needed to calculate the individual thyroid doses on the basis of entered interview data; use this software to calculate doses for a sample of 100 subject.**

Development of software for calculation of individual doses to thyroid based on entered data implements the method of individual dose reconstruction based on thyroid direct measurements of 1986.

To write a subprogram of individual thyroid dose calculation Visual Basic language (DBMS Access 8.0) was used. The basic information for subprogram of calculation is taken from two independent sources: 1 - Moscow DB of direct measurements; 2- DB of interview and radioactive contamination of the environment, called dosimetric DB. While calculating doses two parameters are taken from DB of direct measurements: date of measurements, and corrected thyroid dose rate

The rest of information is taken from dosimetric DB. The content and composition of tables described in [1,2] have been changed because of changes in initial and repeated interview forms.

As a result of subprogram operation for dose calculation received values of individual thyroid doses are filled in the following fields of the Patients Table: DirectDose and EcologicDose, that contain the values obtained on the base of direct measurements data and data of radioecological modelling, correspondingly. Using subject ID obtained doses could be requested and used by other project groups

At present while calculating individual thyroid doses the following suppositions and simplifications are used:

- Contamination of the territory of Belarus with radioiodine is described by one-day fallouts - April 26 in Brest oblast, April 27 in southern part of Gomel oblast, and April 28 in northern part of Gomel oblast and Mogilev oblast [3,4];
- Cows pasture period started prior to the moment of main radioiodine fall outs. Given supposition we have to introduce because in the former interview forms there is no question about the starting date of domestic cattle pasturing;
- Dose received at the cost of inhalation is calculated only for those subjects who deny milk consumption, dairy staffs, and green leaf vegetables in April-May 1986;
- For each cohort subject the starting date of I-131 intake is the date subjects arrival to contaminated territory
- Blocking effect of iodine preparations equal to 2 days following intake;
- Migrations to Vitebsk, Grodno, and Minsk oblasts is considered as ceasing of I-131 intake;
- Age-dependent values of thyroid parameters (mass, constant of effective half-extermination, calibrating factor) are divided into 18 periods and correspond to those presented in Table 24.1.

Table 24.1

Age-depended values of the parameters, used in program for calculation of individual thyroid dose

Age, year	SRP-68-01 calibration factor I-131, Bq per $\mu\text{Rh}^{-1}$	Thyroid mass, g	Effective loss constant of $^{131}\text{I}$ in thyroid, $\text{d}^{-1}$
	$CF$	$m$	$\lambda_{\text{th}}$
0-1	99.5	1.3	0.127
1-2	101.8	1.8	0.120
2-3	103.4	2.3	0.117
3-4	104.8	2.7	0.114
4-5	106.6	3.2	0.111
5-6	109.5	3.9	0.108
6-7	111.3	4.8	0.106
7-8	117.8	5.7	0.103
8-9	122.3	6.6	0.101
9-10	126.5	7.5	0.098
10-11	129.9	8.4	0.096
11-12	132.4	9.3	0.096
12-13	134.5	10.2	0.096
13-14	136.4	11.1	0.096
14-15	138.7	12.0	0.095
15-16	141.7	13.2	0.095
16-17	145.5	14.7	0.095
17-18	150.0	16.2	0.094

Individual thyroid dose of a cohort subject from I-131 is estimated on the base of time-integrated content of I-131 in thyroid:

$$D(T) = \frac{E}{m(T)} * Q \quad (1)$$

when  $D(T)$  - age dependent thyroid exposure dose, Gy;

$E$  - effective energy of decay I-131,  $3.68 \times 10^{-14}$  J Decay $^{-1}$  [6];

$m(T)$  - age dependent thyroid mass, kg; presented in Table 24.1

$T$  - subject age in April-May 1986, years

$Q$  - time integrated content of I-131 in thyroid, Bq s

Calculating formulas describing time-integrated content of I-131 in the thyroid depending on different ways of radioiodine penetration to the body and that are used in the work are presented in [6,7]. In given papers formula (1) is presented in the following way

$$D_m(T) = K_{\text{day}} * E/m(T) * G(T) * F(T) \quad (2)$$

when

$K_{day} = 86400$ , number of seconds in 24 hours,  $d^{-1}$ ;

$G(T)$  – calculated activity of  $^{131}I$  in thyroid, Bq;

$F(T)$  – function describing  $^{131}I$  kinetics in thyroid, d.

$^{131}I$  activity in thyroid at the moment of measurement is calculated in accordance with the following formula IIIЖ

$$G(T) = CF(T) (P_{th} - P_b) \quad (3)$$

when  $CF(T)$  – calculation factor from thyroid dose rate measured by SRP-68-01 to  $^{131}I$  activity in thyroid, Bq per, age dependent values of CF are presented in Table 1

$P_{th}$  – SRP-68-01 readings under thyroid,  $\mu R h^{-1}$

$P_b$  – “background” readings of SRP-68-01,  $\mu R h^{-1}$

Kind of  $F(T)$  function used for calculation of individual dose of the cohort subject is estimated through individual interview and is realized in 12 variants of  $^{131}I$  penetration to the body

In the program of individual dose calculation the following ways of  $^{131}I$  penetration to thyroid are presented

- Inhalative penetration to thyroid

$$F(T) = \exp(L_{Th}(T) * T_m) / L_{Th}(T) \quad (4)$$

when  $\exp$  – exponential function;

$L_{Th}(T)$  – effective loss constant of  $^{131}I$  in thyroid,  $d^{-1}$ , age dependent values of thyroid mass are presented in Table 24.1

$T_m$  – time interval between the date of subject measurement and the starting date of  $^{131}I$  fallouts, d.

- Per oral penetration of  $^{131}I$  with milk during the whole iodine period

$$F(T) = \exp(L_{Th}(T) * T_m) / L_{Th}(T) * (1 / L_c - 1 / L_g) / (1 / (L_c - L_{Th}(T)) * (1 - \exp(-(L_c - L_{Th}(T)) * T_m)) - 1 / (L_g - L_{Th}(T)) * (1 - \exp(-(L_g - L_{Th}(T)) * T_m))) \quad (5)$$

when  $L_c = 0.63$  – constant of biological half decontamination of milk from  $^{131}I$ ,  $d^{-1}$ ,

$L_g = 0.15$  – constant of grass decontamination from  $^{131}I$ ,  $d^{-1}$ ,

- Per oral penetration of  $^{131}I$  with milk without break while taking stable iodine (date of thyroid dose rate measurement is less or equal to the starting date of iodine prophylaxis):

$$\begin{aligned}
F(T) = & \text{Exp}(L\_Th(T) * T\_m) / L\_Th(T) * \\
& (1 / L\_c * (1 - \text{Exp}(-L\_c * T\_b) + \text{Exp}(-L\_c * T\_e)) - \\
& 1 / L\_g * (1 - \text{Exp}(-L\_g * T\_e))) / \\
& (1 / (L\_c - L\_Th(T)) * (1 - \text{Exp}(-(L\_c - L\_Th(T)) * T\_m)) - \\
& 1 / (L\_g - L\_Th(T)) * (1 - \text{Exp}(-(L\_g - L\_Th(T)) * T\_m)))
\end{aligned} \tag{6a}$$

when  $T\_b$  – time interval between starting date of iodine prophylaxis for cohort subject and starting date of fallouts  $^{131}\text{I}$ , d.

$T\_e$  – time interval between final date of iodine prophylaxis for cohort subject and starting date of fallouts  $^{131}\text{I}$ , d

- Per oral penetration of  $^{131}\text{I}$  with milk without break while taking stable iodine (date of thyroid dose rate measurement is more than starting date of iodine prophylaxis but less or equal to the final date of iodine prophylaxis):

$$\begin{aligned}
F(T) = & \text{Exp}(L\_Th(T) * T\_m) / L\_Th(T) * \\
& (1 / L\_c * (1 - \text{Exp}(-L\_c * T\_b) + \text{Exp}(-L\_c * T\_e)) - \\
& 1 / L\_g * (1 - \text{Exp}(-L\_g * T\_b) + \text{Exp}(-L\_g * T\_e))) / \\
& (1 / (L\_c - L\_Th(T)) * (1 - \text{Exp}(-(L\_c - L\_Th(T)) * T\_b)) - \\
& 1 / (L\_g - L\_Th(T)) * (1 - \text{Exp}(-(L\_g - L\_Th(T)) * T\_b)))
\end{aligned} \tag{6b}$$

- Per oral penetration of  $^{131}\text{I}$  with milk without break while taking stable iodine (date of thyroid dose rate measurement is more than the final date of iodine prophylaxis):

$$\begin{aligned}
F(T) = & \text{Exp}(L\_Th(T) * T\_m) / L\_Th(T) * \\
& (1 / L\_c * (1 - \text{Exp}(-L\_c * T\_b) + \text{Exp}(-L\_c * T\_e)) - \\
& 1 / L\_g * (1 - \text{Exp}(-L\_g * T\_b) + \text{Exp}(-L\_g * T\_e))) / \\
& (1 / (L\_c - L\_Th(T)) * (1 - \text{Exp}(-(L\_c - L\_Th(T)) * T\_b) + \\
& \text{Exp}(-(L\_c - L\_Th(T)) * T\_e) - \text{Exp}(-(L\_c - L\_Th(T)) * T\_m)) - \\
& 1 / (L\_g - L\_Th(T)) * (1 - \text{Exp}(-(L\_g - L\_Th(T)) * T\_b) + \\
& \text{Exp}(-(L\_g - L\_Th(T)) * T\_e) - \text{Exp}(-(L\_g - L\_Th(T)) * T\_m)))
\end{aligned} \tag{6c}$$

- Per oral penetration of  $^{131}\text{I}$  with milk was broken because of lack of iodine prophylaxis (date of thyroid dose rate measurement is less or equal to the ceasing date of milk consumption):

$$\begin{aligned}
F(T) = & \text{Exp}(L\_Th(T) * T\_m) / L\_Th(T) * \\
& (1 / L\_c * (1 - \text{Exp}(-L\_c * T\_s)) - \\
& 1 / L\_g * (1 - \text{Exp}(-L\_g * T\_s))) / \\
& (1 / (L\_c - L\_Th(T)) * (1 - \text{Exp}(-(L\_c - L\_Th(T)) * T\_m)) - \\
& 1 / (L\_g - L\_Th(T)) * (1 - \text{Exp}(-(L\_g - L\_Th(T)) * T\_m)))
\end{aligned} \tag{7}$$

when  $T\_s$  – time interval between ceasing date of milk consumption for cohort subject and starting date of fallouts  $^{131}\text{I}$ , d.

- Per oral penetration of  $^{131}\text{I}$  with milk was broken while taking stable iodine (date of thyroid dose rate measurement is less or equal to the ceasing date of milk, date of thyroid dose rate measurement is less or equal to the starting date of iodine prophylaxis):

$$F(T) = \text{Exp}(L_{\text{Th}}(T) * T_m) / L_{\text{Th}}(T) * \\ (1 / L_c * (1 - \text{Exp}(-L_c * T_b)) + \text{Exp}(-L_c * T_e) - \\ \text{Exp}(-L_c * T_s)) - 1 / L_g * (1 - \text{Exp}(-L_g * T_b)) + \\ \text{Exp}(-L_g * T_e) - \text{Exp}(-L_g * T_s))) / \\ (1 / (L_c - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_m)) - \\ 1 / (L_g - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_m))) \quad (8a)$$

- Per oral penetration of  $^{131}\text{I}$  with milk was broken while taking stable iodine (date of thyroid dose rate measurement is less or equal to the ceasing date of milk; date of thyroid dose rate measurement is more than starting date of iodine prophylaxis but less or equal to the final date of iodine prophylaxis):

$$F(T) = \text{Exp}(L_{\text{Th}}(T) * T_m) / L_{\text{Th}}(T) * \\ (1 / L_c * (1 - \text{Exp}(-L_c * T_b)) + \text{Exp}(-L_c * T_e) - \\ \text{Exp}(-L_c * T_s)) - 1 / L_g * (1 - \text{Exp}(-L_g * T_b)) + \\ \text{Exp}(-L_g * T_e) - \text{Exp}(-L_g * T_s))) / \\ (1 / (L_c - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_b)) - \\ 1 / (L_g - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_b))) \quad (8b)$$

- Per oral penetration of  $^{131}\text{I}$  with milk was broken while taking stable iodine (date of thyroid dose rate measurement is less or equal to the ceasing date of milk; date of thyroid dose rate measurement is more than the final date of iodine prophylaxis )

$$F(T) = \text{Exp}(L_{\text{Th}}(T) * T_m) / L_{\text{Th}}(T) * \\ (1 / L_c * (1 - \text{Exp}(-L_c * T_b)) + \text{Exp}(-L_c * T_e) - \\ \text{Exp}(-L_c * T_s)) - 1 / L_g * (1 - \text{Exp}(-L_g * T_b)) + \\ \text{Exp}(-L_g * T_e) - \text{Exp}(-L_g * T_s))) / \\ (1 / (L_c - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_b)) + \quad (8c) \\ \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_e) - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_m)) - \\ 1 / (L_g - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_b)) + \\ \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_e) - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_m)))$$

- Per oral penetration of  $^{131}\text{I}$  with milk was broken without taking stable iodine (date of thyroid dose rate measurement is more than ceasing date of milk consumption):

$$F(T) = \text{Exp}(L_{\text{Th}}(T) * T_m) / L_{\text{Th}}(T) * \\ (1 / L_c * (1 - \text{Exp}(-L_c * T_s)) - 1 / L_g * (1 - \text{Exp}(-L_g * T_s))) / \\ (1 / (L_c - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_s)) - \\ 1 / (L_g - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_s))) \quad (9)$$

- Per oral penetration of  $^{131}\text{I}$  with milk was broken while taking stable iodine (date of thyroid dose rate measurement is more than ceasing date of milk consumption; final date of iodine prophylaxis is less or equal to ceasing date of milk consumption)

$$F(T) = \text{Exp}(L_{\text{Th}}(T) * T_m) / L_{\text{Th}}(T) * \\ (1 / L_c * (1 - \text{Exp}(-L_c * T_b) + \text{Exp}(-L_c * T_e) - \\ \text{Exp}(-L_c * T_s)) - 1 / L_g * (1 - \text{Exp}(-L_g * T_b) + \\ \text{Exp}(-L_g * T_e) - \text{Exp}(-L_g * T_s))) / \\ (1 / (L_c - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_b) + \\ \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_e) - \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_s)) - \\ 1 / (L_g - L_{\text{Th}}(T)) * (1 - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_b) + \\ \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_e) - \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_s))) \quad (10)$$

- Per oral penetration of  $^{131}\text{I}$  with milk was started when subject arrived to contaminated area after fallouts had begun, and then it was broken.

$$F(T) = \text{Exp}(L_{\text{Th}}(T) * T_m) / L_{\text{Th}}(T) * \\ (1 / L_c * (\text{Exp}(-L_c * T_1) - \text{Exp}(-L_c * T_s)) - \\ 1 / L_g * (\text{Exp}(-L_g * T_1) - \text{Exp}(-L_g * T_s))) / \\ (1 / (L_c - L_{\text{Th}}(T)) * (\text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_1) - \\ \text{Exp}(-(L_c - L_{\text{Th}}(T)) * T_s)) - \\ 1 / (L_g - L_{\text{Th}}(T)) * (\text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_1) - \\ \text{Exp}(-(L_g - L_{\text{Th}}(T)) * T_s))) \quad (11)$$

when  $T_1$  – time interval between the date subject arrival to contaminated area and starting date of fallouts  $^{131}\text{I}$ , d.

Subprogram of dose calculation via method of direct measurements as incoming parameters receives the following indices of fields from the table of data base of direct measurements and dosimetric data base:

- Date of thyroid dose rate - field "Meas\_Date";
- Corrected thyroid dose rate (mR/h)
- Information of subject migration in April-May 1986 - terms of staying in the settlement is estimated as difference of two fields of the table Departure86 - "Date". At present, coding is not implemented
- Average daily milk consumption for the period April-May 1986 is calculated from the tables of milk and dairy staffs consumption
- Ceasing date of milk local milk consumption - field "Time\_Stop"
- Starting date stable iodine intake - field "Time\_Block"
- Number of intakes of stable iodine; based on this information ceasing date of stable iodine intake is calculated.

Final result of calculations is field in to the field DirectDose of the Patients Table.

Exposure dose calculation using designed subprogram is performed for 100 subjects presented in the report for the second quarter 1998. Appendix 9 presents the results of

current dose calculation of thyroid exposure dose in comparison with the results of calculation performed in the second quarter and Moscow DB, when

- Dose\_2 – doses calculated in the 2-nd quarter;
- Dose\_4 – doses calculated in the 4-th quarter;
- Dose\_M – doses of Moscow DB.

Milestone 25. Develop and implement calculation procedures to simulate the DP-5 detector response to radiation sources located in the human body for standard and non-standard geometries

*(Dosimetry Group)*

Because of some objective physical reasons A simulation of GM tube response by Monte Carlo method is a challenging problem. Therefore, the work started with preparation of the counter and the probe models, their validation against available experimental information, and a development of the procedure for Monte Carlo simulation of this detector.

Preliminary results achieved in 1998, prior coming to ORNL, were presented in milestone reports of the BelAm study's dosimetry group and in most complete form in [8].

The Monte Carlo simulation of detector response have been performed with the Monte Carlo program MCNP [5] and using such valuable tools as SABRINA [10] and POV-Ray [11]. As in previous work, the model development and visualization efforts in this study were eased considerably by use of various graphical software like SABRINA [10] and POV-Ray [11]. The version of SABRINA ported to Windows 95/NT [7] was provided for current work by Dosimetry Research Group of ORNL. The POV-Ray program was upgraded to a new version, namely version 3.1.

The mathematical human body and thyroid phantoms used in the study are described in [8-10]. As in previous work, the newborn phantom was not considered.

Variance reduction techniques available in MCNP are not applicable to coupled electron-photon transport, thus reducing the number of allowed techniques to those compatible with analog simulation mode. In analog simulations used here to calculate age-dependent calibration factors of DP-5 the only variance reduction technique used was cell-dependent low energy cut-off of electron transport. Also, the source was considered to be  $^{131}\text{I}$  which made possible to get the calibration factor through a single run. Evidently, such source definition would not be possible while simulating the detector response to other radionuclides distributed in the human body. All these problems forced a development of a combined, two-step approach to simulate the detector responses.

The principal idea of the combined approach is to divide the problem space into two regions. In one region the simulation of electron transport is unnecessary and simulation could be performed with higher efficiency and in the second region, which is a region of detector itself, the electron transport is essential to defining the detector response. These two regions are divided by a surface which serves as source surface for the detector. Therefore, the purpose of the first simulation is to collect and preserve information on

particles entering the second (detector) region. MCNP provides for such calculations through the use of 'surface source' option. Under this option MCNP creates a file of particles location, direction, energy, and weight as they cross the surface. This file serves in subsequent runs to provide source particles originating from the surface.

An advantage of such two-step procedure will be observed when running many cases differentiating only by the detector orientation within the source surface. For example, the surface source file is created after simulation of the human body phantom which has a complicated geometry. This is run once. To simulate the detector response then one can use the surface-source already created and make the simulation with simpler geometry of the detector as many times as necessary. Changes of the detector orientation are simulated by spatial transformation of particles tracks recorded in the surface-source file. This means that overall gain from using the two-step procedure would be proportional to the number of detector orientations to be studied within the same source surface.

The results obtained with use of the two-step procedure were compared with previously calculated in single analog runs for QA purposes. Both data sets are compared in Table 25.1. As seen from the table, there is a good agreement between the data sets thus validating the combined, two-step computational procedure.

Table 25.1. Calibration factors of DP-5 to  $^{131}\text{I}$  calculated by two methods,  $\mu\text{Ci h mR}^{-1}$ .

Phantom	single run		two-step run
	$1 \times 10^7$ histories	$2 \times 10^7$ histories	$1 \times 10^7$ histories
1 y	$6.51 \pm 0.38^*$	$6.44 \pm 0.25$	$6.41 \pm 0.38$
5 y	$6.89 \pm 0.42$	$6.94 \pm 0.27$	$6.94 \pm 0.42$
10 y	$8.83 \pm 0.61$	$8.51 \pm 0.42$	$8.59 \pm 0.57$
15 y / female	$9.44 \pm 0.67$	$9.45 \pm 0.46$	$9.51 \pm 0.67$
Adult	$11.26 \pm 0.86$	$11.07 \pm 0.66$	$11.16 \pm 0.85$

\* Error values correspond to  $2\sigma$  confidence interval.

The surface source files generated once for every phantom in the series are then used in simulation of the different detector orientations within the same surface. Among disadvantages of the two-step procedure is the creation of large surface source files. For example, for  $10^7$  histories the generated surface source files vary from 180 to 270 Mbytes in size, depending on phantom.

### *Study of various violations of measurement geometry*

With the two-step procedure described above the calibration factor dependence on the orientation of the detector (rotation) was studied. Fig.25.1 presents geometry for the 1-year old child phantom. This figure represents the cross-section of the phantom and detector in plane  $x=0$ . The standard position for the detector is shown in the figure, i.e. the detector

axis is parallel to lateral dimension ( $x$ -axis) of the human body, and the detector axis is located at the same height as the center of thyroid. The detector's inside is not shown.

The detector has cylindrical external shape which serves as the surface source for the second step. With such surface source it is possible to simulate various detector orientations produced by rotation about the detector axis which is parallel to  $x$ -axis. Because the detector construction allows measurements with open and closed window, each probe location was simulated for both situations. In Fig.25.2, the detector cross-section is shown as well as various rotation angles at which simulation have been performed.

As it is seen from Fig.25.2 the counter is located asymmetrically inside the detector. This is due to the fact that DP-5 detector is based on two GM-counters. The second counter is a low-efficient small GM-counter (see Fig. 3) which is operational at high exposure rates when the first tube (SBM-20) count rate approaches a limit caused by the counter's dead time. It was indicated previously that in real measurements of  $^{131}\text{I}$  activity in thyroid only SBM-20 counter was responsible for the DP-5 response, hence it was the only one considered in the present DP-5 detector model.

Because of the GM-counter placed asymmetrically inside the detector the maximum of the detector efficiency is not observed at standard detector position but rather when the detector is rotated at angle  $\alpha \approx 37^\circ$ , or saying in another words the surface source is rotated at angle  $\alpha \approx -37^\circ$ . This is shown at Fig.25.2 as a black triangle at the lower right corner. Other considered locations are also marked by solid triangles. It seen that due to asymmetry of the probe the total detector rotation angle range studied was from  $-37^\circ$  to  $+217^\circ$ . The calculated angular dependencies of calibration factors for the adult phantom are represented at Figs.25.3 below. Calculated data, having statistical uncertainty within 3 - 5%, are compared with measured results reported by Institute of Biophysics, Moscow (IBP) [17]. These measured data were stated to have uncertainty of 30%. It seen from Fig. 25.3 that calculated and measured data are in a satisfactory agreement for closed detector window while measured points are systematically lower that calculated ones, and for open detector window the disagreement is more.

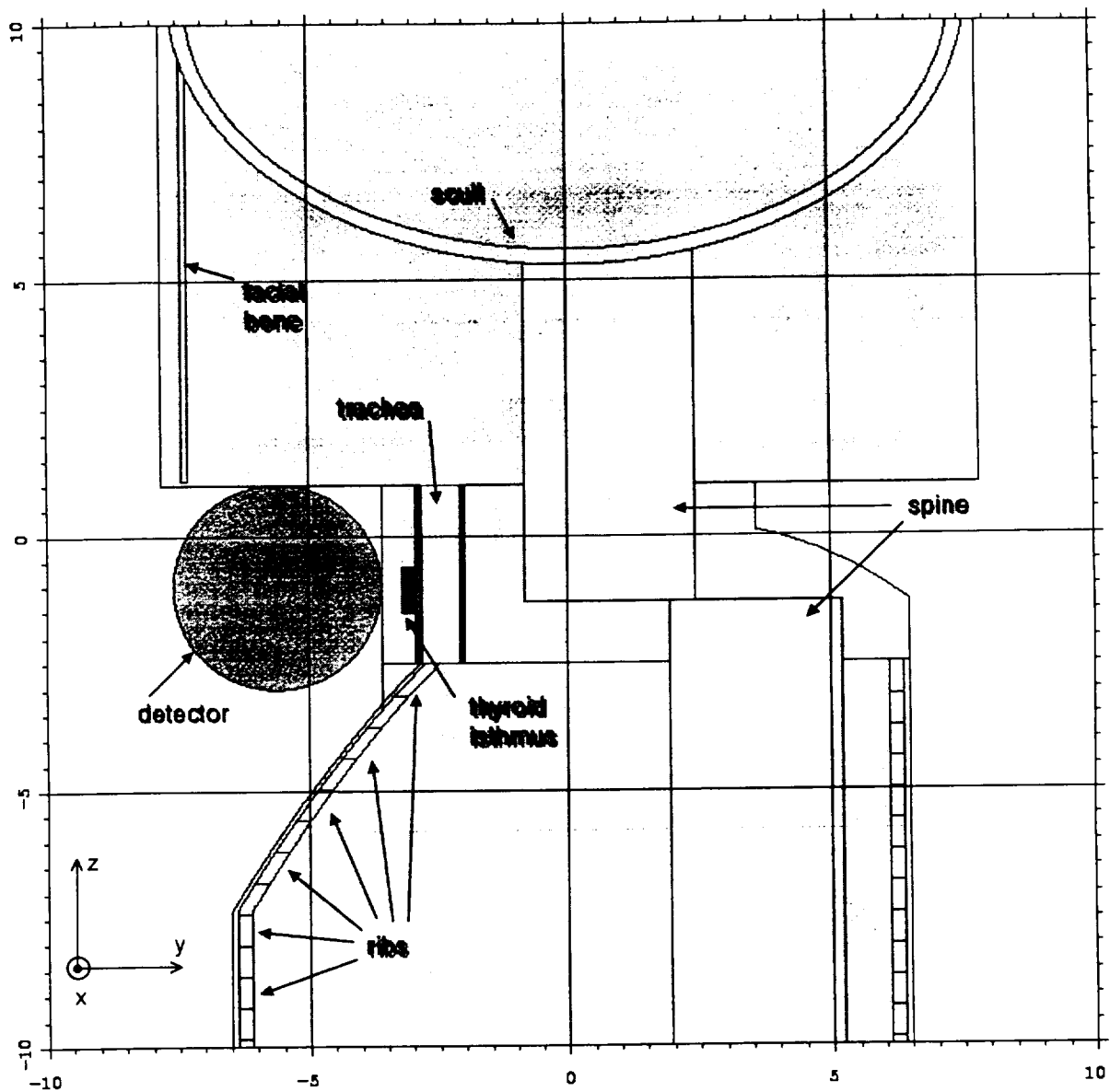


Fig.25.1 MCNP plotting of the 1 year old phantom and the DP-5 detector. Cross-sectional view in the  $x=0$  plane. The detector interior is not shown.

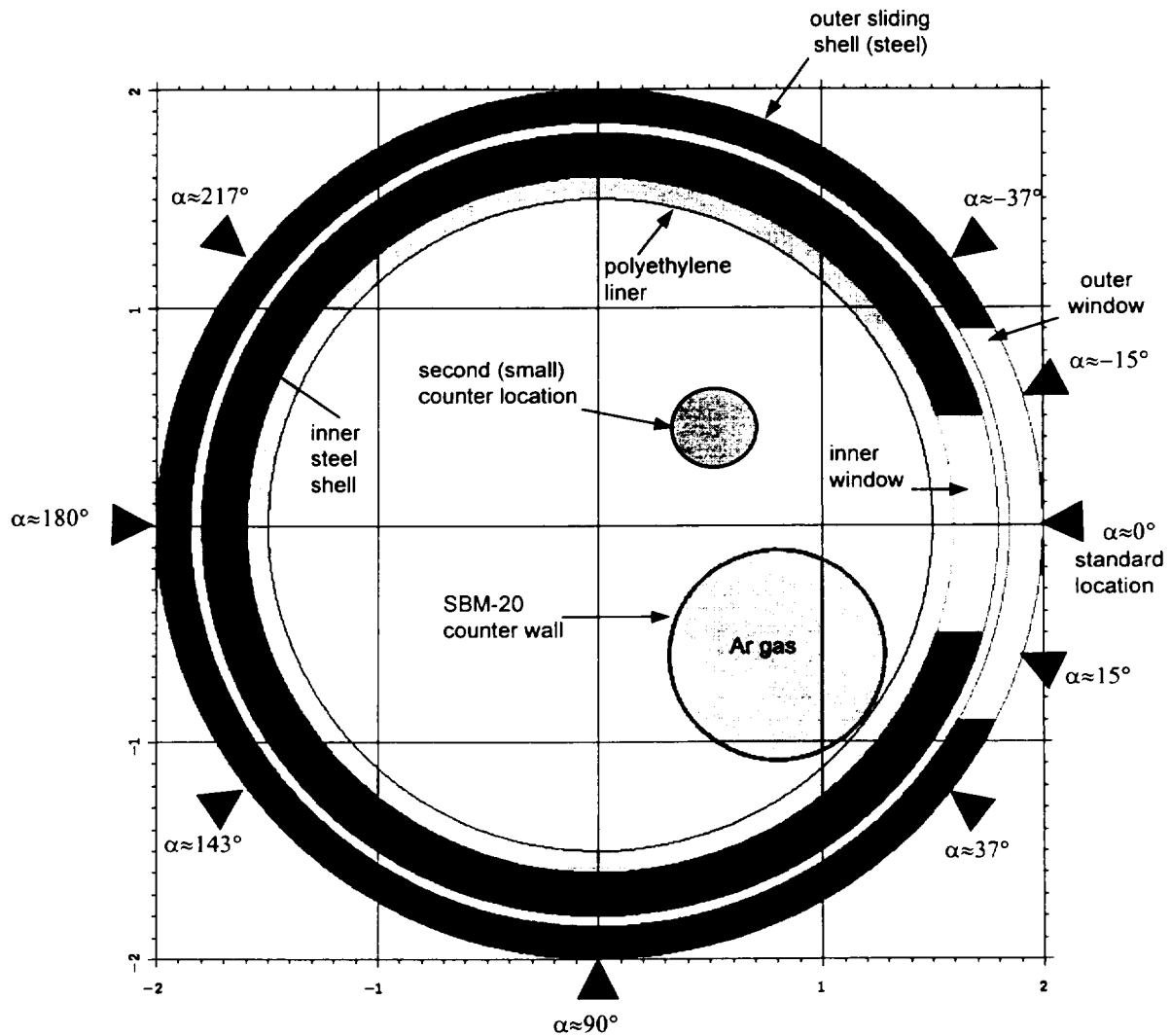


Fig. 25.2. Cross-sectional view of the DP-5 detector model. Window is open. Black triangles indicate directions to center of the source at various rotations of the probe. The detector rotation angles are shown.

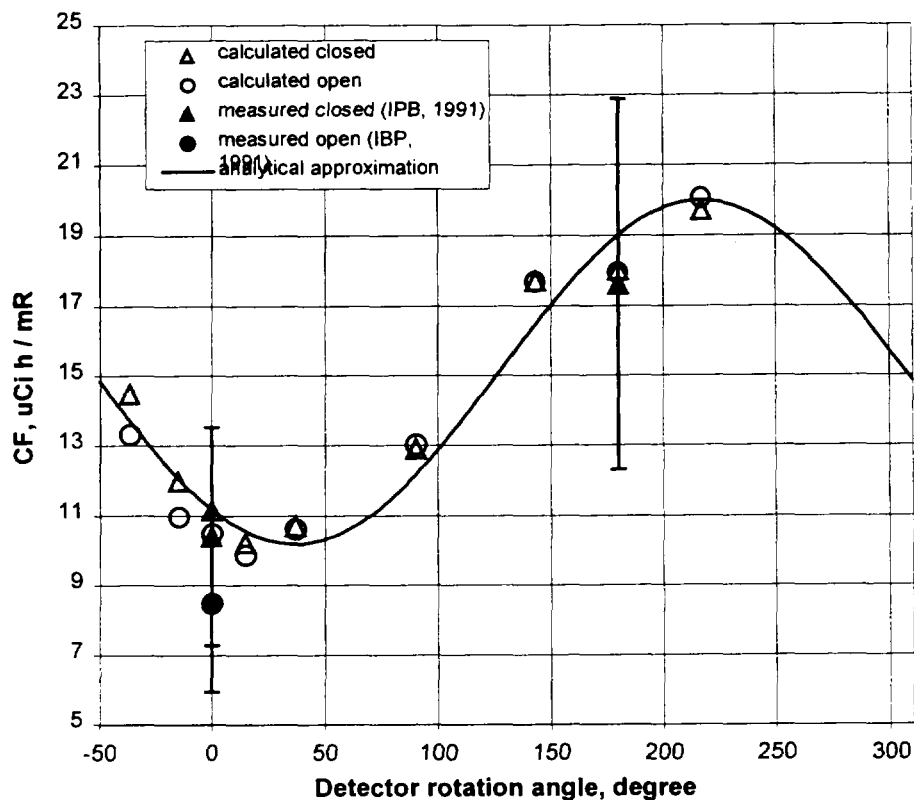


Fig.25.3. Angular dependence of the DP-5 calibration factor for the adult phantom. Error bars are shown only for measured points [11] (solid dots). Calculated points (open dots) have statistical error 3 - 5%.

The calculated data points were fitted by an analytical function of the form:  $f(\alpha) = a \cdot \sin(\alpha - (\frac{\pi}{2} + b)) + c$ , where fitted values of the parameters  $a$ ,  $b$ , and  $c$  are listed in the Table 2 below. The last column in the Table 2 gives a value of a minimum of the analytical angle-dependent calibration factor. This minimum which correspond to a maximum detection efficiency is observed not in the standard detector position but after rotation of the detector at angle  $b$ .

Table 25.2. Parameters of the approximation function for angle-dependent calibration factors.

Phantom	$a, \mu\text{Ci h mR}^{-1}$	$b, ^\circ$	$c, \mu\text{Ci h mR}^{-1}$	$c - a, \mu\text{Ci h mR}^{-1}$
1 y	4.3	37	9.9	5.6
5 y	4.2	37	10.5	6.3
10 y	5.0	37	13.0	8.0
15 y / AF	5.1	37	13.9	8.8
Adult	4.9	37	15.1	10.2

Below at Fig.25.4 calibration factors (detector window closed) calculated for standard position and for position after rotation through an angle  $b$  are plotted. It is seen that rotation at angle  $b$  results in systematically lower calibration factors, which are in a very good agreement with the previous estimate of IBP.

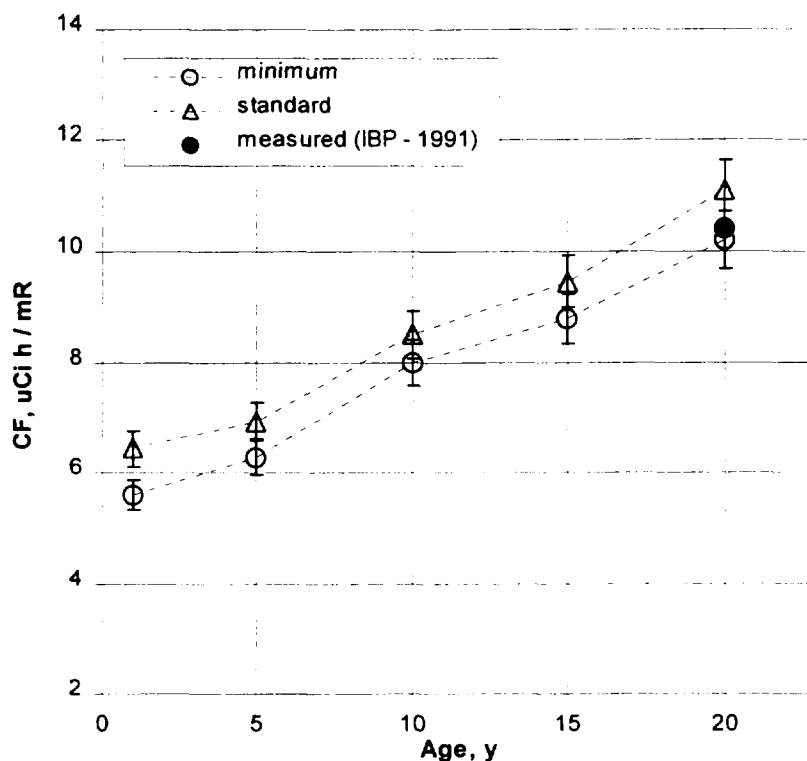


Fig.25.4. Comparison of the DP-5 calibration factors calculated in the detector standard position and minimum calibration factors after detector rotation. It is also shown as a black circle the result obtained by [17].

The model of DP-5 detector allows simulating of the open and closed detector window. The detector response at various angles was studied in both modes. At Fig.25.5 the angle-dependent ratios of calibration factors calculated with open and closed window are shown graphically.

It is seen from Fig.25.5 that the ratios are age-dependent and there is a maximum difference of about 10 % between the detector response with open and closed window. The solid circle in the Fig.25.5 indicates a result derived from data reported by IBP [17] which demonstrates open window effect on calibration factor to be as much as 18 %. That is, the calculated and the measured effects of open window to calibration factors differ approximately 2 times. One explanation of this disagreement could be that calculated responses were produced with surface source (two-step procedure) which includes only photons crossing the detector surface. Is the observed discrepancy due to an absence of electrons in the surface source? To answer this question the analog calculation has been performed for the detector in the standard position with opened window. Unlike previous analog calculations the electron cut-off energies in the thyroid, neck, and trachea were set to be equal 0.1 MeV. Such cut-off was considered to be low enough, because the open detector window does not assume the open counter wall. There is a 1 mm polyethylene liner between the counter wall and the outer space. Such a barrier would effectively prevent low energy electrons from entering the probe. The calculation result had demonstrated that the effect of electrons coming through the open window in the standard

detector position for the adult phantom is not more than 3 % for the  $^{131}\text{I}$ . This means that the discrepancy observed between the calculated and the measured values is not due to the electron contribution, only. The other possible reasons could be:

- the position of the GM counter relative to the window in experiments differs from the position assumed in calculations;
- variations of constitution and age among the group of 73 measured persons, e.g. of thickness of a tissue overlaying the thyroid.

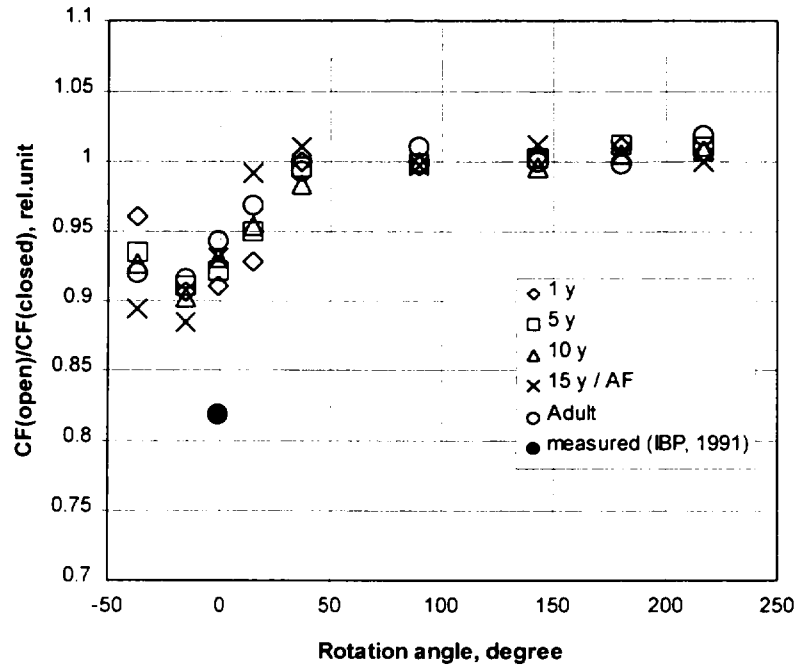


Fig. 25.5. Angle-dependent ratio of DP-5 calibration factors for open and close detector window calculated for various phantom ages.

The next step of the DP-5 detector simulation was to consider an alternative positioning of the probe during measurements. This is referred as an 'orthogonal' position, because the probe is orthogonal to normal position. Such position is very similar to the standard probe position in measurements with NaI detector of SRP-68. Although such position of the detector seemed to be a relatively rare in measurement campaign of 1986, the calibration factor corresponding to 'orthogonal' position should demonstrate most considerable deviation from the standard position. Therefore this case was simulated, too.

The simulation has been performed using the two-step procedure, also. The surface-source file was prepared for the orthogonal position for 5 phantoms in the study and it was used in four runs with the closed detector window looking up, down, left, and right. Results for these four orientations are averaged and presented at Fig.25.6. The calculated points (open circles) are presented with their statistical uncertainty; the solid circle shows the result of IBP [17], its reported uncertainty was 20%.

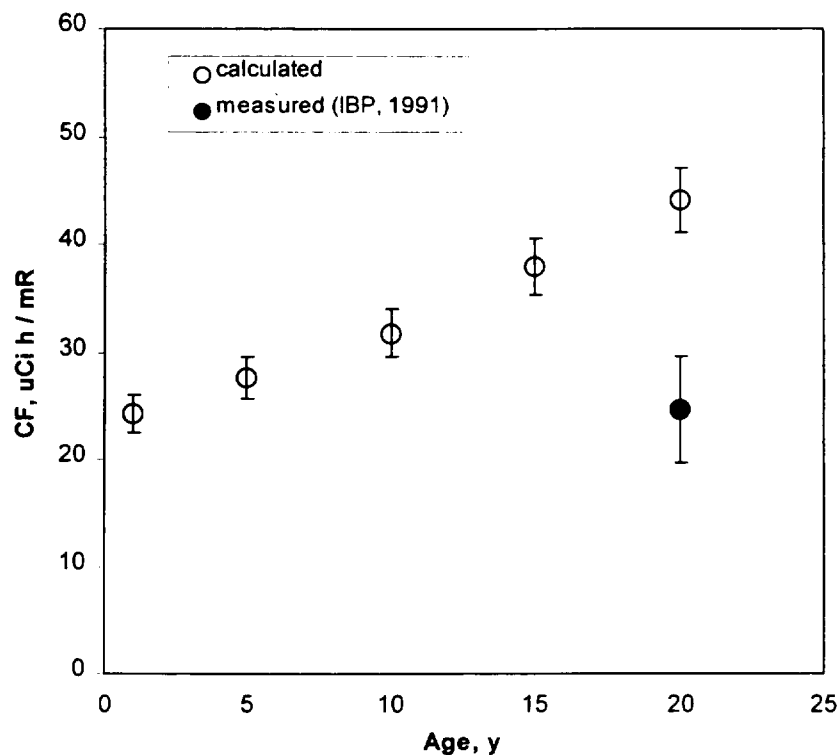


Fig.25.6. Age-dependent calibration factors of DP-5 for orthogonal position of the detector.

It is seen from Fig.25.6 that the calculated and the measured points disagree far beyond their uncertainty limits. The reason of such a discrepancy has to be verified because of the value of the discrepancy (factor of 2) would introduce a considerable error to dose estimates in cases when the measurements were known to be performed with the detector in the orthogonal position.

The possible origin of the disagreement noted in Fig.25.6 could be deficiencies in either the computational procedure or the measured data (e.g. caused by a contribution from activity in the whole body, or by a greater uncertainty due to a decrease of detection efficiency in orthogonal geometry). Therefore, the calculated data were checked and verified. This was done by running a series of analog simulations for sources of various geometry. The main idea of the check was to compute a ratio of the calibration factors in 'normal' and 'orthogonal' positions. As it can be seen from Fig.25.6 and data in Table 25.2, the 'orthogonal-to-normal' ratio for the adult phantom is 2.4 for measured data and 3.9 for calculated data. Therefore, this ratio was calculated for the given detector model for a number of cases which are described below.

The sources considered were: 1) a parallel beam in air; 2) single point source in air; 3) two point sources in air; 4) two point sources in water cylinder representing the neck; 5) two elliptical volume sources (thyroid lobes) in water cylinder. Such selection of source geometry should account for major effects influential to the detector response when the problem geometry goes from simplest case (parallel beam) to realistic (volume source in water) case. In Table 25.3 below the main results are presented. To understand these numbers and especially the considerable difference between  $^{131}\text{I}$  and  $^{60}\text{Co}$  in the geometry

of parallel beam, the energy dependence of the efficiency have been calculated for cases A and B with monoenergy photon sources. Results are shown at Fig. 25.7 and 25.8 below. The absolute efficiency per particle per MeV is presented at Fig. 8 for parallel beam and isotropic point source in both locations 1 and 2 (see Table 25.3).

Table 25.3. Ratios of calibration factors for a number of simple sources in two locations corresponding normal (1) and 'orthogonal' (2) placement of the DP-5 detector.

Case	Source geometry <sup>a</sup>	Description	Ratio 'orthogonal' / normal	
			$CF_2 / CF_1 \equiv \eta_1 / \eta_2$	
			<sup>131</sup> I	<sup>60</sup> Co
A		Parallel beam	$3.87 \pm 0.33^b$	$2.36 \pm 0.09$
B		Single point isotropic source	$3.67 \pm 0.31$	$3.47 \pm 0.13$
C		Two point isotropic sources in free air	$3.54 \pm 0.31$	$3.48 \pm 0.13$
D		Two point isotropic sources in water cylinder	$3.09 \pm 0.25$	$3.43 \pm 0.14$
E		Two elliptical volume sources in water cylinder	$3.95 \pm 0.35$	$4.21 \pm 0.19$

<sup>a</sup> 1 - normal detector position, 2 - 'orthogonal' position

<sup>b</sup> all listed errors correspond to 1 standard deviation

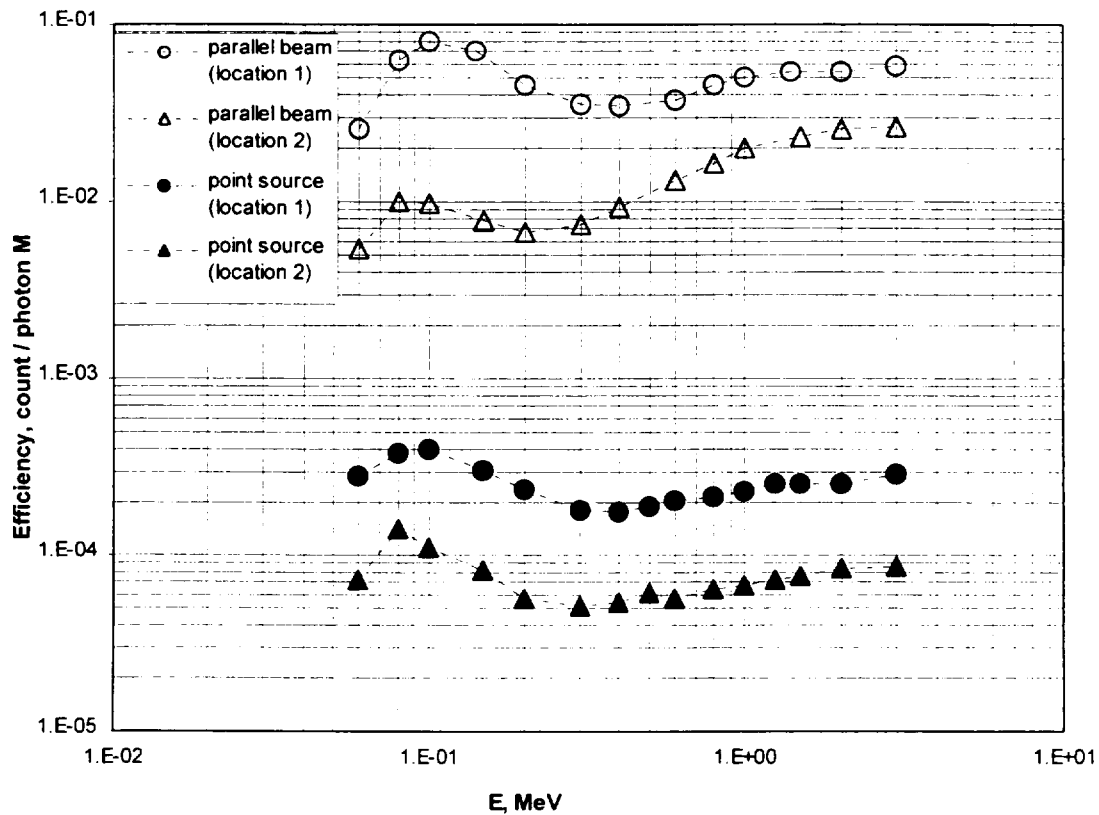


Fig.25.7. Comparison of the energy-dependent DP-5 efficiency in two geometries, namely, a parallel monoenergy beam (open points) and isotropic point source (solid points), for two locations of the source (see Table 25.3 for details).

It is seen from the data presented in Fig.25.8 that energy-dependent efficiencies demonstrate similar behavior. However, the parallel beam points demonstrate different energy dependence in location 1 and 2, while point source energy dependence for both locations is almost the same.

To make differences in energy dependence more clear, the ratios of the data presented at Fig.25.7 are plotted at Fig.25.8. It became clear that plotted ratios have very different energy dependence in the energy range below 0.4 MeV. That is, while the point source ratio is approximately constant, it varies within 3 and 4, the ratio for the parallel beam varies from 2 to 9. From data presented at Fig.25.9 it is evident why the ratios listed in the Table 25.3 for case A (parallel beam) for  $^{131}\text{I}$  and  $^{60}\text{Co}$  are different while other ratios are approximately the same.

The data calculated and presented in Table 25.3 and Figs. 25.7 and 25.8 increase our confidence in the calculated DP-5 calibration factors for 'orthogonal' location of the detector. Nevertheless, the additional simulations could not prove the validity of the calculated data, because the detector model is simplified comparatively to the real detector. There is a speculation that the results observed in the case of ideal parallel beam incident along the axis of cylindrical model of the detector are just computational artifacts caused

by idealization of the detector structure and the beam geometry. Furthermore, truly parallel beam sources do not exist in the real world.

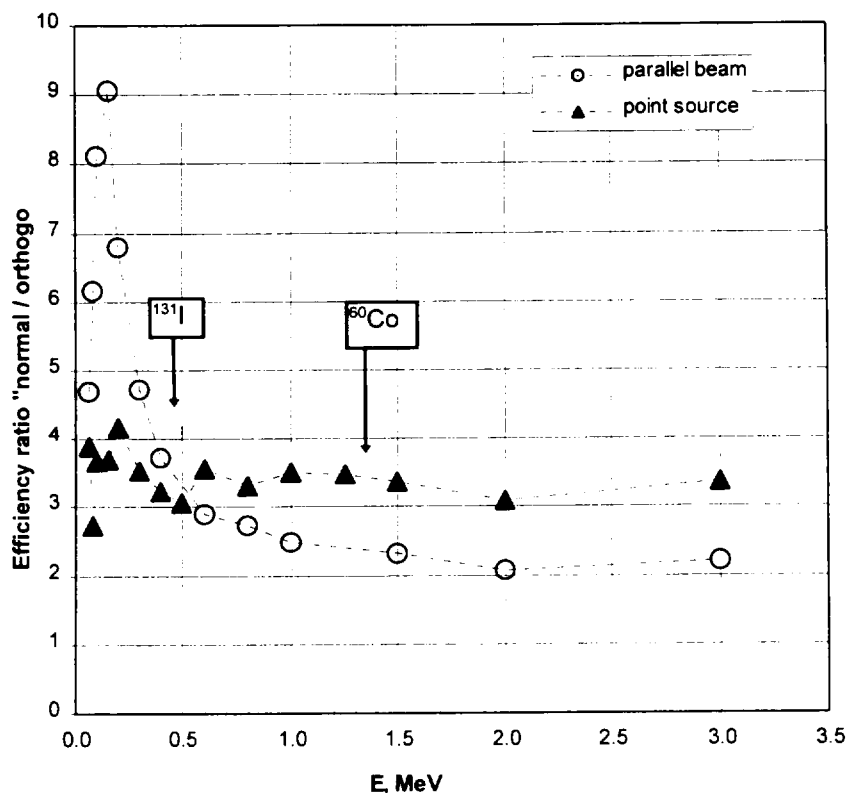


Fig. 25.8. The energy-dependent ratio of the DP-5 efficiencies to monoenergy isotropic point source and parallel beam in locations referred as 1 and 2 (see Table 25.3 for details).

To resolve this issue independent experimental data could be used. Such data could be obtained by measuring the detector response to several standard radioactive sources placed at different locations relatively the detector. Previous measurements undertaken in 1993 in Institute of Radiation Medicine in Minsk did not succeed because of low sensitivity of DP-5 to the available standard radioactive sources. Therefore, would experiments be performed again they should be made at a standard calibration facility in the geometry of pencil beam or with point sources of higher activity. Such measurements followed by Monte Carlo simulation of the current idealized detector model in real measurement conditions would be invaluable to validate the simulation approaches.

Another reason to undertake an experimental work with the DP-5 dose-rate meter is that the available experimental data are sparse and unique. Therefore, the new experimental data could be a reliable basis to resolve the above mentioned discrepancies between the simulated data and measured ones as well as they would make a solid basis for validation and improvements of the detector model provided the latter would be shown necessary.

The year 1998 visit to ORNL has resulted in a significant progress in calculation of the DP-5 characteristics which were unknown before. These include age-dependent calibration factors for a variety of geometrical conditions.

Two-step simulation approach was developed to allow more efficient simulation of the DP-5 gas-discharge detector response. The use of the two-step procedure had considerably reduced computational expenses, e.g. an estimated gain in overall computational performance is about of factor of 10.

The DP-5 responses were calculated under various geometrical conditions and impact of the detector rotation was estimated. The source considered was  $^{131}\text{I}$  in thyroid. The number of considered cases was doubled by simulation of the detector with open and closed window. The results of calculations were analyzed and presented in the analytical form convenient for further use in the dose assessment.

The comparison with available experimental data had been made where possible. The calculated data have shown good agreement with available measurements for closed window, the only measured point for detector with open window was less approximately 10% than the computed data. The discrepancy is observed between calculated and measured data for the detector placed orthogonal to the standard position. The only available measured value is 44% less than calculated one.

The calculated calibration factors in the orthogonal detector position were indirectly verified in a series of analog simulations covering various source geometries from simplest parallel beam to thyroid-like volume sources. Results of these simulations have increased the confidence in the calculated DP-5 calibration factors for orthogonal detector position. However, need for alternative independent high quality experimental data to resolve the observed discrepancy is evident. Such experimental work should be undertaken prior coming to the next extensive calculations for radioactive sources other than  $^{131}\text{I}$  distributed throughout the human body.

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## **APPENDIX**

Progress of disease: Not ☐, if Yes ☐, specify:

nodule growth ☐, new nodule ☐, metastasis ☐, location

\_\_\_\_\_

Combination with other thyroid pathology Not ☐, if Yes ☐, specify:

\_\_\_\_\_ IDC-9 \_\_\_\_\_

**5. Lymphadenopathy:** Not ☐, if Yes ☐, specify:

Left side ☐, Right side ☐, both sides, ☐ Central ☐  
Possibly related to regional infection: Yes ☐ No ☐

**6. Parathyroid abnormality:**

Yes ☐ No ☐ Suspected ☐

Hypofunction ☐ hyperplasia ☐

Hyperfunction ☐ Adenoma ☐

other diagnoses \_\_\_\_\_

\_\_\_\_\_ IDC-9 \_\_\_\_\_

## RECOMMENDATIONS

**1. NEXT VISIT IN A YEAR :** Not ☐, if Yes ☐, specify:

IN \_\_\_\_\_ MONTHS Date of expected visit \_\_\_\_\_

Day Month Year

Referral to hospital (Acsakovschina): ☐ \_\_\_\_\_

Day Month Year

Referral to NCTOP ☐ \_\_\_\_\_

Day Month Year

Other referrals (hospital or polyclinic): ☐

Polyclinic #: \_\_\_\_\_ Pediatric ☐ Adult ☐

**2. TREATMENT: MEDICATIONS** Not ☐, if Yes ☐, specify:

A. Levothyroxine ☐ Dose \_\_\_\_\_

B. Thyrostatic preparations ☐ Dose \_\_\_\_\_

B. Stable iodine ☐ Dose \_\_\_\_\_

F. Other ☐ Dose \_\_\_\_\_

Comments: ↓

\_\_\_\_\_

Code - Name of Physician: \_\_\_\_\_

Signature of physician \_\_\_\_\_

Code

QC expert signature ☐ \_\_\_\_\_

Expert-specialist ☐ \_\_\_\_\_

Head of Screening Centre ☐ \_\_\_\_\_

Comments ↓:

\_\_\_\_\_

Entered to computer: ☐, Code of operator \_\_\_\_\_

**Hospital, RCIRME**

**1. Date of hospitalization from** [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] **to** [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]  
Day Month Year Day Month Year

3. Initially revealed , ☐, if previously ☐ date |\_\_|\_|\_|\_\_|\_|\_|\_\_|\_|\_|\_|

[illegible]

(suspecion :|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_| ID C-9 |\_|\_|\_|\_|\_|)|

Type, variant: | | | | | | | | | | | | | | | | | | | | | |

**Thyroid degree :** | | **Function:** | | | | | | | | | | | | | | | |

Nodule/tumor location: right lobe ☐, left lobe ☐, isthmus ☐

nodule specificity: | | | | | | | | | | | | | | | | | | | | , T| | | |N| | | |M| | | |

(USE ☐, Cytology ☐)

surgery: No ☐, because of main disease ☐, because of other disease ☐: IDC-9 |\_\_|\_\_|\_\_|,|\_\_|

Nosology: | | | | | | | | | | | | | | | | | | | | | |

**Location:** right side ☐, left side ☐, isthmus ☐

Total      times,    Date: 1).                          2).                         

amount of surgery: TTE ☐, STTE ☐, HTE ☐, if other specify: \_\_\_\_\_

Posts - surgical treatment No ☐, if yes ☐, specify \_\_\_\_\_

**Gammatherapy :**                      Dose |\_|\_|\_|\_|                      Date |\_|\_|\_|\_|\_|\_|\_|\_|\_|

Radioiodine therapy:                  Dose |\_|\_|\_|\_|\_|                  Date |\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|

Complications following surgery: Not ☐, if Yes ☐, specify: IDC-9 |\_\_|\_\_|\_\_|,|\_\_|

Progress of disease: Not ☐, if Yes ☐, specify:

nodule growth ☐, new nodule ☐, metastasis ☐, location

Combination with other thyroid pathology Not ☐, if Yes ☐, specify:

[illegible]

Nosology: \_\_\_\_\_

**5. Disagreement with screening diagnosis:** Yes ☐ Not ☐

**6. Other diagnoses(exact copy):**

### Diagnoses (text)

IDC-9

1) 

| | | | | | | | | | | | | | | | | | | | | |

\_\_\_\_\_

2)     |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_| |\_|

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Name and code of Physician |\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_|\_\_\_\_\_| (Signature)

(Passed with copy of Summary)

QC expert signature ☐ [ ] [ ] [ ] ,  
 Expert-specialist ☐ [ ] [ ] [ ] ,  
 Head of Screening Centre ☐ [ ] [ ] [ ] ,

Comments ☐ ↓:

Entered to computer: ☐, Code of operator ☐☐☐

# HOSPITALIZATION FORM NCTOP

ID

1. Date of hospitalization from       to        
Day Month Year Day Month Year

2. № medical chart

3. Referral from Clinic RCIRME ☐

Screening center ☐

4. Main diagnosis: IDC - 9

Nosology:

Location: right lobe ☐, left lobe ☐, isthmus ☐

T  N  M  (for thyroid cancer)

Comments:

Combinations with other thyroid pathology: IDC - 9

6. Disagreement of main diagnosis at the time of deferral:

Not ☐, if Yes ☐,

7. Other diagnoses(exact copy):

Diagnose (text)

IDC - 9

1)

2)

8. Surgery No ☐, Yes ☐,

If No, specify reason: refusal ☐

no need ☐

Other:

If Yes,

For the first time ☐, repeated surgery ☐, totally ☐ time

Date of current surgery:

Day Month Year

-total thyroidectomy		<input type="checkbox"/>	
- subtotal thyroidectomy			<input type="checkbox"/>
- hemithyroidectomy		<input type="checkbox"/>	
-modified neck dissection including vien			
	one side		<input type="checkbox"/>
	both side		<input type="checkbox"/>
- radical neck dissection			
	one side		<input type="checkbox"/>
	both side		<input type="checkbox"/>
- paratracheal dissection			
	one side		<input type="checkbox"/>
	both side		<input type="checkbox"/>

both side 

Other | \_\_\_\_\_  
\_\_\_\_\_

Total dose      |\_\_|\_\_|\_\_|\_\_|

Other: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

12. fine needle Biopsy, No ☐, If Yes ☐ Date        
Day Month Year

[illegible]

|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|  
 (Code of Physician)

(Signature)

1 1 1 1,

[illegible]

Entered to computer: ☐, Code of operator

## ID

Hystological number(s) \_\_\_\_\_

Fixed ☐

Paraffin blocks ☐ Hystological slides ☐

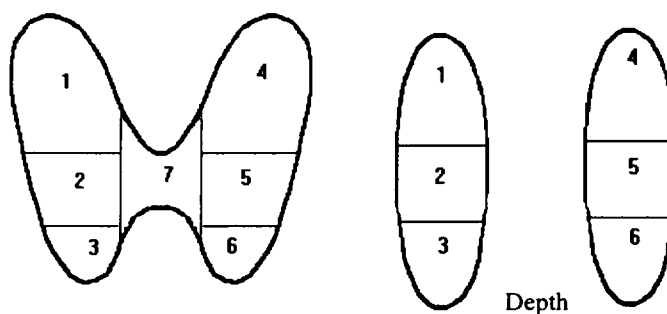
### Primary documentation of macroscopic examination ☐

## 1. MACROSCOPIC EXAMINATION

### 1.1.THYROID TISSUE

	WEIGHT (g)	Size (mm)			CONSISTENCY
Right lobe					
Left lobe					
Isthmus					
Right lobe + Left lobe					
Left lobe + Isthmus					
Thyroid Nodule					

### 1.2. Thyroid nodules (localization with mark on diagram)

[illegible]

consistency:										
• soft (elastic)										
• flabby										
• dense										
• very dense										
Condition:										
• homogeneous										
• heterogeneous										
• thyroid tissues										
• with white taint										
Crystal changes										
• absent										
• completely										
• partially										

## 1.3. Lymph nodes

Number: single ☐ several (2-3) ☐ many (>3) ☐  
 Localization: neck ☐ rightside ☐ leftside ☐ central ☐  
 upper./mediastenal ☐ non identified ☐

## 2. HISTOLOGICAL EXAMINATION

## 2.1 THYROID TISSUE

Follicles: macrofollicular ☐ colloid cysts ☐  
 normofollicular ☐ solid ☐  
 microfollicular ☐

Epithelium: FUNCTION CELL CONTENT  
 hypo ☐ A-cells ☐  
 norm ☐ B-cells ☐

Strome: sclerosis yes ☐ no ☐ if yes  
 focal ☐ weak ☐  
 diffusive ☐ moderate ☐  
 strong ☐  
 inflammatory infiltration yes ☐ no ☐ if yes  
 Focal ☐ Diffusive ☐ Granulomatosis ☐  
 other deviations (specify)

## 2.2. Thyroid nodules

	right lobe				left lobe				isthmus	
	1	2	3	4	1	2	3	4	1	2
Hyperplastic (adenomatous)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adenoma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hystological type Variant										
Carcinome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hystological type Variant										

Additional hystological signs of tumor:

Necrosis	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
<b>Mitoses</b>	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
FNA traces	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Psammom bodies	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Strom sclerosis	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Dermoid cellular transformation	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Light cellular transformation	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Mucine	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Amiloid	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Oxifilar cells	Yes <input type="checkbox"/>	No <input type="checkbox"/>		

**INVASIVE GROWTH:** yes ☐ no ☐ if yes

node capsules ☐ blood vessels ☐

lymph nodes ☐ gland capsules ☐

surrounding tissue ☐ other ☐

### 2.3. Lymph nodules

normal ☐

hyperplastic ☐

metastatic carcinoma ☐

Neck ☒ -rightside ☐ leftside ☐ central ☐  
upper/mediastenal ☐ non identified ☐

Histological form \_\_\_\_\_  
Extranodal growth of tumor ☐

### 3. CONCLUSION

[illegible]

## pTNM CARCINOME CLASSIFICATION

T	_____	(X,0,1a,1b,2a,2b,3a,3b,4a,4b)
N	_____	(X,0,1a,1b)
M		(X,0,1)

Name of pathomorphologist |\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|

Name of expert | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_ | \_

difference in opinions    yes    ☐    no    ☐ if yes specify

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

Expert's signature \_\_\_\_\_

## OPERATIONAL MANUAL FOR QUALITY ASSURANCE

### General statements

One of practical tasks of BelAm Project is to get acquainted the specialists with quality assurance procedure of medical study.

The aim of Quality Assurance is to obtain objective information through standardization of the process and minimizing of errors of objective and subjective nature. To implement this it is necessary to solve the following tasks:

- design Operational Manual (OM) of Project,
- prepare standard forms,
- train and certify personnel,
- quality control (QC) of equipment,
- QC of performed procedures
- QC of made decision
- QC of information collection and processing

Design of Project OM and standard forms is performed before the Project start. But at the initial stage of the study (during first three years) they could be updated and modernized. Updated forms and OM are dated and stored in the form of interim documents. Any changes are registered by DCC. Administration and Group Leaders should be provided with text of OM and informed of all changes.

Personnel training is performed prior to their work in the Project, and in case when changes made to OM. This training suggests acquaintance with principals and tasks of the Project, with corresponding Sections of OM, including documents and instructions for their completion. Following training names of specialists, dates and certification status are registered. All information is stored in DB of personnel (DCC). DCC informs Group Leaders about the necessity of recertification. Terms of certification of different groups of specialists are given in OM.

QC of equipment is based on the following data: list of equipment used at specific stage of the study, regulations for control under the technical state of each piece of equipment pointing out the periodicity of the control and reference to current document reflecting technical state of equipment, QC reports (Annex) submitted to DCC in standard form and in fixed terms.

QC of procedure, as a rule, envisage direct survey under the implementation of this procedure and its comparison with the description in corresponding Section of OM. One should remember that at the stage of examination there could be few procedures (for example, collection of sample, its storage, transportation, test) and each of them should be under separate control.

While performing QC of made decision an estimation is made whether this decision corresponds to criteria of OM. Making decision means the following: identification of subject, giving status to cohort subject, making diagnosis, referral to hospitalization,

estimation of laboratory tests, cytological and pathomorphological conclusion, etc. All disagreements appeared in the course of the Project should be studied by experts to reveal the reasons and make agreed decision.

In QC of data collection and processing one should take into account the correspondence of subject's passport data with those marked at bar-code label; follow all the instructions for forms completion, perform manual coding and editing for completeness of all fields, use IDC codes described in OM. To estimate the quality of data cross logic comparison is used. There is also studied a compatibility of data from different specialists and their equipment.

Quality Assurance has multilevel nature. Responsibility for its performance is laid on examiners themselves (self-control), Group Leaders, Project Administration, expert including international, QC expert, DCC, and incharged persons. The results of QC are put to the Form of QC Report.

## Appendix 6.

**Data of Individual Interview Form***Instruction for filling in*

*Individual Interview Form is completed by interviewer during initial interview of examinee ("E") and his accompanies. Given form is primarily designed for interviewing parents of examinee. But if only examinee is presented He/She should be asked all the questions regardless the age. But if for "E" it is difficult to answer this or that question interviewer should not press him/her.*

*Procedure of interview.*

1. Put the date of interview.
2. Mark with "x" symbol participants of interview.
3. Put family name of "E". If at the time of the accident "E" had another family name, put it below.
4. Put the name of "E".
5. Put the patronymic of "E".
6. Put the date of birth of "E".
7. Mark with "x" symbol sex of "E".
8. Put detailed current address of "E". Do not make any comments on right fields regarding from what time "E" reside given address.
9. Put address of "E" at the time of the accident.
- 9a. Mark with "x" symbol from what material walls of building where "E" lived at the time of the accident were made.
- 9b. Put the floor where "E" lived at the time of the accident.
10. Mark with "x", if "E" was evacuated (moved him/herself) from the place of residence (place of staying at the time of accident) in the period 26.04 - 31.05.86.
11. Put in the table information of "E" movements in 1986 following the accident from the place of residence (place of staying at the time of the accident). Special attention should be paid to the period of 26.04 -31.05. It is necessary to record in details the rout of "E" movements in that period including week ends and holidays trips.

In the field "movements in 1986" put Oblast, Rajon, Settlement (place, if it was summer camp, sanatorium, rest house etc.).

In the field "duration of staying" should be put the duration of staying in mentioned settlement, i.e. in field "from" put date of arrival (day, month) and in field "to" date of departure (day, month)

If "E" can not remind more or less exact date of arrival, interviewer should use suggested code, that should be put to field "code". So code shows approximate date of arrival to given settlement. The date of departure will be the date (code) of arrival to another mentioned settlement etc.

If "E" moved to a new place of residence, in the field "PPR" put "x". symbol

To the line "time of staying outdoor" the information should be put the following way:

If "E" suggests as an answer interval estimation of time of staying outdoor, put it correspondingly to field "from" and "to".

If "E" suggests as an answer exact number of hours of outdoor staying put it to field "from", field "to" will be empty.

12. Put to the table information of 'E' movements from the place of residence for the period of 24 days and more in the following years.

In the field "Where" put Oblast, Rajon, Settlement (place, summer camp, sanatorium, rest house etc) of movement.

In the field "Year of movement" put the year of movement.

If 'E' moved to a new place of residence, in the field "PPR" put "x" symbol.

In the field "duration of staying" put the duration of staying (in months) in the mentioned settlements. If 'E' moved for the period from 24 days to 1 months, consider it as a movement for the term of 1 month.

Do not put information of movements for the period of less than 24 days below the table. Do not make any comment on the fields.

13. Mark with "x" symbol appropriate variant of answer.

Questions 14-14d refers to the place of residence (place of staying at the time of the accident).

14. Put how many hours 'E' usually spent outdoor in spring and summer period before the accident.

If "E" suggests as an answer interval estimation of time of staying outdoor, put it correspondingly to fields "from" and "to".

If "E" suggests as an answer exact number of hours of outdoor staying put it to field "from", field "to" will be empty.

14a. Mark with "x" symbol appropriate variant of answer

Do not suggest to 'E' variant "do not remember" as a possible answer.

14b. If 'E' could remind more or less exact date when staying outdoors was limited put it.

If for 'E' it is difficult to remind exact date, mark appropriate variant with "x" symbol.

14c. During what period this limitation continued. Do not forget to record in what units 'E' mentioned the term (days, weeks).

14d. Put how many hours 'E' usually spent outdoor in the period of limitation.

If "E" suggests as an answer interval estimation of time of staying outdoor, put it correspondingly to fields "from" and "to".

If "E" suggests as an answer exact number of hours of outdoor staying put it to field "from", field "to" will be empty.

15. Pay attention that this question deals with the period of 26.04 - 31.05.86.

15a. Mark with "x" symbol appropriate variant of answer

Do not suggest to 'E' variant "do not remember" as a possible answer

15b. It is necessary to receive from 'E' the following information

1. When did 'E' start taking stable iodine;
2. Did 'E' take them daily;
3. During what period did 'E' take them

If 'E' could remind more or less exact starting date of stable iodine intake mark it in the calendar for April-May 1986 it.

If for 'E' it is difficult to remind exact date, mark appropriate variant with "x" symbol.

Record whether 'E' took stable iodine daily, if no - how many times a week.

Record during what period 'E' took stable iodine Do not forget to record in what units 'E' mentioned the term (days, weeks).

15c. Mark with "x" symbol appropriate variant of answer

16. Pay attention that this question deals with 'E' regular milk consumption before the accident.

Using suggested codes put to the table information of milk consumption the following way.

In the field "what milk" record appropriate variant of K1 code.

In the field "source" record appropriate variant of K2 code.

In the field "how many liters for one intake" record the quantity of milk (in liters) that 'E' consumed for one intake.

In the field "how many times per day" record how many times per day 'E' consumed milk

In the field "how often" record appropriate variant of K3 code.

16a. Pay attention that this question deals with 'E' regular milk consumption in the period of 26.04 - 31.05.86.

Mark with "x" symbol appropriate variant of answer

Do not suggest to 'E' variant "do not remember" as a possible answer 15a.

Take into account that answer variant "no" means that 'E' continued to drink milk from the same source and in the same quantity during the whole mentioned period.

Using suggested codes put to the table information of milk consumption in the period of 26.04 - 31.05.86 the following way.

In the field "what milk" record appropriate variant of K1 code.

In the field "source" record appropriate variant of K2 code.

In the field "settlement" . If 'E' in the period of 26.04 - 31.05 moved from the place of residence, this field should correspond to the field "movements in 1986" of 11 item. If 'E' did not move during the mentioned period, to the field "settlement" put the place of residence.

Field "period of consumption". This field should reflect changes in milk consumption in the period April-May 1986. The following variants are possible.

1. "E" in the period April-May 1986 did not move from the place of residence but quitted milk consumption in the mentioned period. If 'E' could remind more or less exact date of quitting of milk consumption put this date to the field "from" to the field "to" put the date 26.04.86. If for 'E' it is difficult to remind the date, so use suggested K4 code that should be put to the field "code". The code shows approximate date of quitting of milk consumption.

2. "E" moved from the place of residence, but quitted milk consumption prior to movement. Information is put the same way as in previous variant.

3. "E" moved from the place of residence and before movement continued milk consumption. In this case date of quitting of milk consumption is considered as a date of movement.

Information of milk consumption in the places to which 'E' moved is put the following way.

If "E" consumed milk, in fields "from" ("code") and "to", correspondingly, information is put corresponding to the date of arrival and departure from the given settlement.

If in places ( or in some of them) where 'E' moved 'E' did not consumpt milk, fields "from", "to", and "code" will remain empty.

If 'E' quitted milk consumption, to the field "from" date of arrival to given settlement is put, and in the field "to" the date of quitting of milk consumption is put.

If for 'E' it is difficult to remind exact date, use suggested K4 code

In the field "how many liters for one intake" record the quantity of milk (in liters) that 'E' consumpt for one intake.

In the field "how many times per day" record how many times per day 'E' consumpt milk

In the field "how often" record appropriate variant of K3 code.

16b. Using previous table record the date (correspondingly - code) of quit of milk consumption. It is very important to put the date correctly.

What date consider the date of quitting of milk consumption?

Date of departure from the place of residence (place of staying at the time of the accident), if «E» consumpted milk before departure and moved outside contaminated area or was taken to summer camp, sanatorium, rest house, etc.

Date of quitting of milk consumption, if «E» did not move from the place of residence or quitted milk consumption before movement.

Starting date of milk substitutes consumption, i.e. date when "E" quitted fresh milk consumption and started dry, concentrated or condensed milk.

16c. If "E" could remind more or less exact starting date of pasture of home cow (goat) in spring 1986, record this date (day, month.

If for "E" it is difficult to remind a date chose the variant from suggested list and mark with "x"symbol appropriate variant of answer

Do not suggest to 'E' variant "do not remember" as a possible answer

If 'E' remember that during the period 26.04 - 31.05.86 cow (goat) was not pastured (fed by hay), in this case mark the variant "end of may and later".

17. Pay attention that this question deals with the period of 26.04 - 31.05.86.

Mark with "x"symbol appropriate variant of answer

17a. If 'E' could remind more or less exact date when breast feeding was quitted put this date (day, month).

If for 'E' it is difficult to remind exact date, mark appropriate variant with "x"symbol.

18. Pay attention that this question deals with the period of 26.04 - 31.05.86.

Mark with "x"symbol appropriate variant of answer

Do not suggest to 'E' variant "do not remember" as a possible answer

18a. Complete the table the following way.

In the field "type of food staff" chose those food staffs 'E' consumpted

In the fields "how many times a day" and "how many times a week" record how often 'E' consumpted given food staff

If "E" suggests as an answer interval estimation of time of staying outdoor, put it correspondingly to fields "from" and "to".

If "E" suggests as an answer exact number of hours of outdoor staying put it to field "from", field 'to' will be empty.

In the field "how much for one consumption" record how much 'E' consumed given food staff per one intake and in the field "units of measurement" record units of measurement (grams or litters)

19. Pay attention that this question deals with 'E' consumption of green leafy vegetables in the period of 26.04 - 31.05.86. in the place of residence (place of staying at the time of the accident). Do not consider green leafy vegetables if they were cooked

Mark with "x" symbol appropriate variant of answer

19a. Fill in the table the following way

In the field "type of green leafy vegetable" record appropriate variant of K1 code. If 'E' consumed several types of green leafy vegetables (glv) list them below and put the information to the table separately for each type of glv.

In the field "source of consumed glv" record appropriate variant of K2 code. Take into consideration that imported glv means glv bought in a store. It mostly belongs to 'E' who lived in cities. GIV from private farm, dacha, local markets refers to glv of local production.

In the field "starting date of consumption" put the information the following way.

If 'E' could remind more or less exact starting date of consumption of mentioned type of glv, put this date to field 'date'

If for 'E' it is difficult to remind date, use suggested K3 code that should be put to field 'Code'

In the field "amount of consumed glv" record what amount of glv (approximately) 'E' consumed a day (grams).

In field "how often" record appropriate K4 code.

20. Record regular daily ration (grams) of 'E' at present.

Do not make comments how many times a week 'E' consumed given type of staff as question refers to daily ration.

20a. It means mushrooms consumption at mushroom period and consumption of cooked mushrooms. Mark with "x" symbol appropriate variant of answer.

21. If in medical records there is an information of 'E' WBC examination (WBC -whole body counter - a device in the form of armchair that is used for estimation of radioactive contact in the human body), put it in to the suggested table the following way.

In the field "where" record name medical institution and settlement where examination was performed.

In the field "height" record height of 'E' at the time of examination.

In the field "weight" record weight of 'E' at the time of examination.

In the field "when" record month and year of examination..

In the field "activity" record measured activity

In the field "units of activity" record units of measured activity (мкCi, nCi, kBq, other).

If you record information of WBC examination from the words of 'E' complete only field "where" of the given table

22. Ask whether 'E' undergone annual x-ray or fluorogrpigic examination regularly. Mark with "x" appropriate variant. If the answer is "yes", record from what year.

22a. Ask whether 'E' undergone specialized x-ray examination. Mark with "x" symbol appropriate variant. If the answer is "yes", complete the table.

226. Complete the table the following way.

In the field "what part of body" record code corresponding to part of body.

**In the field "when " record month and year when x-ray was made.**

**In the field "where" record medical institution where x-ray was performed.**

**23. Ask whether 'E' undergone diagnostical examination with radio pharmacological preparations (radio pharmacological preparation - is radioactive preparation that is given to the patient for diagnostical purposes, for example, examination of kidneys function, thyroid etc.) Mark with "x" symbol appropriate variant. If "yes", complete the table.**

**23a. Complete the table the following way.**

**In the field "what body organ" record code corresponding to body organ.**

**In the field "when" record month and year when 'E' undergone diagnostical examination with radio pharmacological preparations.**

**In the field "when" record name of medical institution where radiopharmacological diagnostics was performed**

**24. Ask whether 'E' was subjected to medical exposure with therapeutic reasons.**

**Mark with "x" symbol appropriate variant. If "yes", complete the table.**

**24a. Complete the table the following way.**

**In the field "when" record month and year when 'E' was subjected to medical exposure with therapeutic reasons..**

**In the field "when" record name of medical institution where 'E' was subjected to medical exposure with therapeutic reasons**

Strictly follow instruction for filling in interview form

Stay in the framework of suggested form of answers recording, do not make any marks and comments on the fields

*After completion the Initial Interview Form should be passed to*

*\_\_\_\_\_ and stored in the Dosimetry Laboratory*

Draft 20.12.98

APPENDIX 7

## INITIAL INTERVIEW FORM

Patient's bar-code

1. Date of inquiry:

Day	Month	Year
<input type="text"/>	<input type="text"/>	<input type="text"/>

2. Code of questioned person:

Self-examined	<input type="checkbox"/>	
Mother	<input type="checkbox"/>	
Father	<input type="checkbox"/>	Other relatives <input type="checkbox"/>
Sister, brother	<input type="checkbox"/>	Others <input type="checkbox"/>

3. Surname of subject:

Surname at the time of the accident:

4. First name of subject:

5. Patronymic of subject:

6. Date of birth:

Day	Month	Year
<input type="text"/>	<input type="text"/>	<input type="text"/>

7. Sex : male ☐female ☐

8. CURRENT HOME ADDRESS:

OBLAST

RAYON

SELSOVET

SETTLEMENT

STREET/HOUSE/APPT

PHONE

9. ADDRESS AT THE TIME OF THE ACCIDENT:

OBLAST

RAYON

SELSOVET

SETTLEMENT

STREET/HOUSE/APPT

9a. Type of residence:

wood	<input type="checkbox"/>	panel	<input type="checkbox"/>
brick	<input type="checkbox"/>	other	<input type="checkbox"/> <input type="text"/>

9b. What floor did you live? 

10. Were you, evacuated or moved yourself during the period of April-May 1986?

yes	<input type="checkbox"/>	no	<input type="checkbox"/>
-----	--------------------------	----	--------------------------

((Codes for column "Duration of staying": end of April=1, beginning of May =2, middle of May =3, end of May and later =4)).

[illegible]

Item 11:	good	satisfactory	unsatisfactory
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**12.** Did you move out the place of residence for more than 24 days and change of place of residence in the following years:

[illegible]

13. Did you attend a school or pre-school facility in 1986?

kindergarten ☐ school ☐ did not attend ☐

14. How much time did you spend outdoors in spring and summer time before the accident (hours per day)?

Spring from  to  Summer from  to

14a. Did you limit the amount of time you spent outdoors after the accident, in comparison to your usual habits at this time of the year?

yes ☐ no ☐ (move to i. 15) do not remember = 3 ☐ (move to i. 15)

14b. When did you limit staying outdoors?:

Day  Month

If exact date is not known, please, chose some from the following:

end of April ☐ beginning of May ☐  
middle of May ☐ end of May and later ☐

14c. For how long did this limitation continue (weeks, days (underline))?

14d. How much time (hours) did you spend outdoors during limitation?

From  to

Item 14-14d: good ☐ satisfactory ☐ unsatisfactory ☐

15. Iodine prophylaxis carried out in April-May 1986:

yes ☐ no ☐ (move to i. 16)

do not remember ☐ (move to i. 16)

15a. Kind of iodine preparation:

antistrumine ☐ (white small pill sweet)  
thyroidine ☐ (small pill sweet)  
thyroxin ☐ (white small pill)  
iodinealcohol solution ☐ (iodine for wounds treatment)  
some drops of iodine with water or milk ☐  
iodine to the skin ☐  
lugol solution ☐  
KI ☐  
do not remember ☐

15b. Point the day when you started taken iodine preparations?

April-May 1986

MO	Tu.	we	Th.	Fr	sa	su
					26	27
28	29	30	1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

If you do not remember, choose appropriate answer from the following variants:

end of April ☐ beginning of May ☐  
middle of May ☐ end of May and later ☐

How long did you use them:

daily ☐ several times a week ☐ how many times?

During what period of time did you take iodine preparations (how many weeks, days (underline))?

15c. Who conducted the iodine prophylaxis?

Independently ☐ local physicians ☐  
in the place of evacuation ☐ physicians in hospital ☐

Item 15-15c: good ☐ satisfactory ☐ unsatisfactory ☐

16. Using suggested codes, put the information about milk consumption before the accident in to the table:

Codes	
Milk: (K1)	cow = 1 goat = 2 mother = 3; milk blend = 4 powder milk = 5
Source: (K2)	from private farm = 1 from local dairy = 2 from store = 3 in preventive clinic = 4
How often: (K3):	every day = 1 few times a week = 2 few times a month = 3 did not consumt = 4 <input type="checkbox"/>

Milk (code K1)	Source (code K2)	Litres per one consumption	Times per day	How often (code K3)
		<input type="text"/>		
		<input type="text"/>		
		<input type="text"/>		

16a. Did you change consumption of milk in April-May 1986?

yes ☐ no ☐ (move to i.16c) do not remember ☐ (move to i.16c)

Using suggested codes, put the information about milk consumption in the period of April-May 1986 in to the table:

Codes	
Milk: (K1)	cow = 1 goat = 2 mother = 3; milk blend = 4 powder milk = 5
Source: (K2)	from private farm = 1 from local dairy = 2 from store = 3 in preventive clinic = 4
How often: (K3):	every day = 1 few times a week = 2 few times a month = 3
Period following the accident): (K4)	end of April = 1 may holidays = 2 after May holidays = 3 end of May, June = 4

Milk (code K1)	Source (code K2)	Settlement	Date (from-to) (if exact date is unknown put K4 code)			Litres per one consumption	Times per day	How often (code K3)
			from	to	Code			
						<input type="text"/>		
						<input type="text"/>		
						<input type="text"/>		

16b. Date of quitting of milk consumption \_\_\_/\_\_\_/86.

If the exact date is unknown, choose appropriate answer from the variants given below:

end of April ☐ beginning of May ☐  
middle of May ☐ end of May and later ☐ do not remember ☐

16c. Starting date of cattle pasturing in 1998: \_\_\_/\_\_\_/86.

If the exact date is unknown, choose appropriate answer from the variants given below:

end of April ☐ beginning of May ☐  
middle of May ☐ end of May and later ☐ do not remember ☐

17. Did you consume your mother's milk in April-May 1986?

yes ☐ no ☐ (move to i.18)

17a. When breast feeding was quited:

Day   Month

If the exact date is unknown, choose appropriate answer from the variants given below:

end of April ☐ beginning of May ☐  
middle of May ☐ end of May and later ☐ do not remember ☐

Item 16-17a: good ☐ satisfactory ☐ unsatisfactory ☐

18. Consumption of milk products (food) in April-May 1986?

yes ☐ no ☐ (move to i.19)

do not remember ☐ (move to i.19)

18a. Put in the table the information about consumption of milk food after the accident April-May 1986:

Food	Times per day		Times per week		Amount per one consumption	Unit of measure
	from	to	from	to		
milk soup (kasha)						
sour milk						
kefir						
soft cheese						
sour cream						
butter						

Item 18-18a: good ☐ satisfactory ☐ unsatisfactory ☐

19. Consumption of green leafy vegetables in April-May 1986:

yes ☐ no ☐ (move to i. 20) do not remember ☐ (move to i.20)

19a. Using suggested codes, put the information about consumption of green leafy vegetables in April-May 1986 in to the table:

Codes	
Green leafy vegetable (K1)	parsley, dill = 1 lettuce = 2 sorrel = 3 spring onions = 4
Source (K2)	locally produced = 1 trucked in = 2
Period after the accident (K3)	end of April = 1 beginning of May = 2 middle of May = 3 end of May = 4
How often (K4)	every day = 1 a few times a week = 2 a few times a month = 3

Green leafy vegetable (K1)	From what source (K2)	Date of the beginning (if exact date is unknown put K3 code)	Amount	How often (K4)
		__/__/__		
		__/__/__		
		__/__/__		

20. Your casual daily food allowance (current):

\_\_\_\_|\_\_\_\_|litres of milk \_\_\_\_|\_\_\_\_|grams of potato \_\_\_\_|\_\_\_\_|grams of meat

20a. Do you eat local mushrooms regularly:

yes ☐ no ☐

21. How often were you examined with a whole-body counter

Medical facility, settlement	Height, cm	Weight, kg	When		Activity	Units of activity
			month	year		
			____	19____		
			____	19____		
			____	19____		

22. Did you undergo regular roentgenologic and fluoroscopic examinations?

yes ☐ starting what year \_\_\_\_|\_\_\_\_| where \_\_\_\_|\_\_\_\_|  
no ☐

yes ☒ no ☐ (move to i.23)

[illegible]

yes ☐ no ☐ (move to i. 24)




[illegible]

yes ☐ no ☐

When (month)	When (year)	Where (medical facility, settlement)

[illegible]

good ☐ satisfactory ☐ unsatisfactory ☐

	Code
	<input type="text"/>
	<input type="text"/>
	<input type="text"/>

## APPENDIX 8.

### Individual Interview Form

#### *Instruction for data entry.*

Data entry from paper "Individual Interview Form" to computer data base is performed by operator. Data base is implemented in Microsoft Access DBMS. After opening of DB via Microsoft Access a window will appear on the screen with two fields for entry: **Name** and **Password**. To open DB operator should enter his/her name and personal password. After keying of password a window will appear on the screen **Screening Data Entry**, chose the button "**individual Interview**". Furthermore on the window **Enter patient's code** enter indentificational code of the subject and date of interview (day, month, year). Data entry form will appear on the screen. Number, name, numeration of fields in the data entry form corresponds to Individual Interview Form.

*Procedure of data entry.*

1. **Date of interview.** Entered. Check correctness of entry.
2. **Participants of interview.** To mark the participants of interview put mouse pointer to appropriate variant of answer and click mouse button.
3. **Surname of subject and Surname at the time of accident.** Entered from initial form. Check correctness of entry.
4. **First name of subject.** Entered from initial form. Check correctness of entry.
5. **Patronymic.** Entered from initial form. Check correctness of entry.
6. **Date of birth.** Enter to the field the date (day, month, year).
7. **Sex.** To enter sex put mouse pointer to the button of variants and click the mouse. Choose necessary sex. Your choice will be entered to the window.
8. **Current home address.** In the field **Oblast** call for list of oblasts. To do this put mouse pointer to the button of variants and click the mouse. Choose necessary oblast. Your choice will be entered to the window of given field. In the field **Rajon** call for list of rajons. From suggested list chose appropriate rajon. . In the field **Settlement** call for list of settlements. From suggested list chose appropriate settlement. To the fields, **Street, House, Building, Apartment, Phone** text information is keyed.

If at present subjects lives outside Belarus put his/her address in field **Address outside Belarus** as text information.

9. **Address at the time of the accident.** In the field **Oblast** call for list of oblasts.. Chose necessary oblast. Your choice will be entered to the window of given field. In the field **Rajon** call for list of rajons. From suggested list chose appropriate rajon. . In the field **Settlement** call for list of settlements. From suggested list chose appropriate settlement. To the fields, **Street, House, Building, Apartment, Phone** text information is keyed.

If at present subjects lives outside Belarus put his/her address in field **Address outside Belarus** as text information..

- 9a. **Type of residence.** Point appropriate variant of answer. If the variant is "other, in the field **other specify** put text information.

- 9b. **What floor did you live.** Numerical information is entered to the field.

10. **Were you evacuated or moved yourself during the period of April- May 1986**  
Choose appropriate variant.

To start the next group of questions press the button **Move to i. 11-12.**

**11. Migrations from the place of residence in 1986.** To enter the information into the fields **Oblast, Rajon, Settlement, Place of rest** use the button of pictogram with envelope. A window will appear on the screen **Address entry**. In the field **Oblast** call for list of oblasts.. Chose necessary oblast. Your choice will be entered to the window of given field. In the field **Rajon** call for list of rajons. From suggested list chose appropriate rajon. . In the field **Settlement** call for list of settlements. From suggested list choose appropriate settlement. To the field **Place of rest in Belarus** text information is keyed. To exit from the window press **OK** button.

Movements outside Belarus in 1986 are entered into the **Address (outside Belarus)** as text information.

**Duration of staying.** Date of arrival (day, month, year) is entered into the field **From**, Date of departure is entered into the field **To**. To the field **Code** numerical information is entered..

If subject moved to new place of residence point it in the field **Place of Residence**

**Time spent outdoors.** Into the fields **From, TO** numerical information is entered

In the field **Estimation (Item 11)** call for list of estimates. Choose appropriate one from suggested list..

**12. Movement outside place of residence for more than 24 days and change of place of residence in the following years.** Pay attention! You should not enter information from the field of the table **Where to (Oblast, Rajon, Settlement)**

Into the field **Year** numerical information is entered

If subject moved to a new place of residence point it in the field **Place of residence**

Into the field **Duration of staying** numerical information is entered.

To start the next group of questions use pictogram i13-14d.

**13. Did you attend a school or pre-school facility in 1986. Point appropriate variant of answer.**

**14. How much time did you spend outdoors before the accident. To the fields From and To numeric information is entered.**

**14a. Did you limit the amount of time you spent outdoors after the accident. Choose appropriate variant of answer.**

**14b. When did you limit staying outdoors. To the fields From and To numeric information is entered. If exact date is unknown chose appropriate variant of answer**

**14c. For how long did this limitation continue. Put numeric information and units of measurement (days or weeks)**

**14d. How much time did you spent outdoors during limitation. To the fields From and To numeric information is entered.**

In the field **Estimation (Item 14-14d))** call for list of estimates. Choose appropriate one from suggested list..

**15. Iodine prophylaxis carried out in April-May 1986** Choose appropriate variant of answer.

**15a. Kind of iodine preparation.** Choose appropriate variant of answer.

**15b. Point the date when you started taken iodine preparations. To the field a date is entered. If exact date is unknown chose appropriate variant of answer.**

**How often.** Choose appropriate variant. If answer several times a week, into the field **How many times** enter numeric information.

During what period of time did you take iodine preparations. **Put numeric information and corresponding unit of measurement (days or weeks)**

*15c. Who conducted the iodine prophylaxis. Choose appropriate variant.*

*In the field Estimation (Item 15-15c ) call for list of estimates. Choose appropriate one from suggested list..*

**To start the next group of questions use pictogram i.16\_17a.**

**16. Using suggested codes fill into the table information of milk consumption before the accident** Numerical information is entered to all fields of the table

*16a. Did you change consumption of milk in April-May 1986 1986. Choose appropriate variant of answer.*

*Using suggested codes put to the table information of milk consumption in the period of April-May 1986. To the fields What milk (code K1) and Source (code K2) numerical information is entered. In the Field Settlement text information is entered. Into the fields From and To Terms of milk consumption date is entered (day, month, year), into the field code – numeric information. Into the field Litters per one consumption, Times per day, How often numeric information is entered.*

*16b. Date of quitting of milk consumption. To the field a date is entered (day, month, year) If exact date is unknown chose appropriate variant of answer.*

*16c. Starting date of cattle pasturing in 1986. To the field a date is entered (day, month, year) If exact date is unknown chose appropriate variant of answer*

*17. Did you consume breast milk in April-May 1986. Choose appropriate variant of answer*

*17a. When breast feeding was quitted To the fields Day and Month numeric information is entered. If exact date is unknown choose appropriate variant of answer*

*In the field Estimation (Item 16-17a) call for list of estimates. Choose appropriate one from suggested list..*

*18. Consumption of milk products in April-May 1986. Choose appropriate variant of answer*

**18a. Complete the table with the following information. In to the field food call for list of food staffs. From suggested list choose corresponding food staffs. In the field units of measurement call for list of units of measurement. Choose appropriate units of measurement. In the rest fields of table enter numeric information**

*In the field Estimation (Item 18-18a) call for list of estimates. Choose appropriate one from suggested list..*

**19. Consumption of green leafy vegetables (glv) in April-May 1986. Choose appropriate variant of answer**

*19a. Using suggested codes put the information of consumption of glv in April-May 1986 into the table. Into all fields of table, except field Date numerical information is entered. Into the field Date date is entered (day, month, year)*

*20. Your casual daily food allowance(current). Into all fields numerical information is entered*

*20a. Did you eat local mushrooms Chose appropriate variant of answer*

*To start the next group of questions use pictogram i.21\_24.*

**21. How often were you examined with a WBC. Into the field Where text information is entered. Into the fields Height, Weight, Month, Year, Activity numerical information is entered. In the field Units of measurement call for list of units. From suggested list choose appropriate units.**

22. *Did you undergo regular x-ray or fluoroscopic examination* Choose appropriate variant. If Yes, into the field *Starting what year* enter numeric information

22a. *Did you undergo x-ray specialized examination.* Choose appropriate variant

22b. *How many times.* Into the fields *Organ, Month, Year* numerical information is entered. Into the field *Where* text information is entered.

23. Did you undergo diagnostic examination with the use of radiopharmaceuticals. Choose appropriate variant.

23a. *How many times.* Into the fields *Organ, Month,*

*Year* numerical information is entered. Into the field *Where* text information is entered

24. *Did you undergo radiation treatment* Choose appropriate variant

24a. *When and where did you undergo radiation treatment..* Into the fields *Month and Year* numerical information in entered. Into the field *Where* text information is entered

*Into the field Interview was conducted by surname of interviewer is*

**In the field** quality estimation of conducted interview **call for list of estimates.** Choose appropriate one from suggested list.

**Exit from the data entry form saving entered information is performed via Exit button located in upper right corner of screen.**

**Exit without saving of entered information is performed via Cancel button.**

**Entry of the next form is performed via Choose subject. Button.**

## APPENDIX 9.

Table. Comparison of the results of thyroid dose calculation.

№	Surname	Name	Patronymic	Age	D <sub>m</sub> , sGy 4 q.	D <sub>m</sub> , sGy 2 q.
49689	КИРИЛЕНКО	ОЛЕГ	ПЕТРОВИЧ	99	94,3	70
5970	ПАВЛЕНКО	АЛЕКСЕЙ	ЛЕОНИДОВИЧ	25	26,7	30
12323	ЛАНЧЕНКО	АЛЕКСАНДР	ПЕТРОВИЧ	275	26,3	40
19711	БУЙНЕВИЧ	ГАЛИНА	ВИКТОРОВНА	62	62,9	50
23528	ГРЕСЬ	ВЛАДИМИР	НИКОЛАЕВИЧ	66	60,6	50
38763	ЛИХОШАПКО	СЕРГЕЙ	ЛЕОНИДОВИЧ	49	48,2	50
18938	САКОВСКИЙ	ИГОРЬ	ПЕТРОВИЧ	49	156,9	90
36940	МАРТЫНЕНКО	РОМАН	ПЕТРОВИЧ	61	61,6	50
121948	ПЫРСИКОВА	НАДЕЖДА	ВЛАДИМИРОВ	54	57,5	70
108879	АНИСЕНКО	ВАСИЛИЙ	ИВАНОВИЧ	36	33,0	30
171865	ФЕШЕНКО	ЗОЯ	ВАСИЛЬЕВНА	34	36,6	40
179423	ПЕТРЕНКО	ИВАН	ПЕТРОВИЧ	52	49,1	60
197006	БАРТНОВСКИЙ	ЮРИЙ	НИКОЛАЕВИЧ	30	30,5	30
39555	МИСКЕВИЧ	ЕЛЕНА	НИКОЛАЕВНА	49	52,3	60
39293	БОБРОВНИЧИЙ	ВАСИЛИЙ	ВИКТОРОВИЧ	61	55,7	30
39370	ДАЙНЕКО	ДМИТРИЙ	ВАСИЛЬЕВИЧ	50	49,6	50
147471	ХОДУНЬКО	ВИКТОР	ИВАНОВИЧ	62	66,2	70
196218	КОШЕПЕВ	АЛЕКСАНДР	АЛЕКСАНДРОВ	0,75	0,8	0,4
131561	РУДОМИНА	АНТОНИНА	АНАТОЛЬЕВНА	0,35	0,3	0,1
44694	ИВАНОВА	ОКСАНА	СЕРГЕЕВНА	0,39	0,4	0,5
82339	НОВИЦКИЙ	СЕРГЕЙ	ВАЛЕРЬЕВИЧ	0,63	0,6	0,62
88104	БОЦУЛА	КОНСТАНТИН	НИКОЛАЕВИЧ	1	1,0	1,04
87531	ФИЛИПЕНОК	АЛЕКСАНДР	ЛЕОНИДОВИЧ	0,54	0,5	0,55
78306	КОРЕНЕВ	ЕВГЕНИЙ	ВЛАДИМИРОВ	1,85	1,7	1,88
78191	КОНОНЕНКО	НАТАЛЬЯ	ВАЛЕНТИНОВ	0,79	0,8	0,82
78190	КОНОНЕНКО	ЕЛЕНА	ВАЛЕНТИНОВ	0,62	0,6	0,74
87532	ФИЛИПЕНОК	СЕРГЕЙ	АЛЕКСАНДРОВ	1,84	1,6	1,83
72842	ВАЛУЕВИЧ	НАТАЛЬЯ	АНАТОЛЬЕВНА	0,91	0,9	0,92
74309	ГУРЧЕНОК	ЕЛЕНА	ЮРЬЕВНА	0,86	0,9	1,05
72376	ВАСИЛЕВСКИЙ	АЛЕКСЕЙ	ВАЛЕРЬЕВИЧ	0,75	0,9	0,87
71607	БОНДИКОВ	АЛЕКСАНДР	АЛЕКСАНДРОВ	0,32	0,3	0,35
70971	БАРМИНА	ЛАРИСА	ВИТАЛЬЕВНА	1,22	1,2	1,23
70831	БАКУМЕНКО	ОКСАНА	НИКОЛАЕВНА	1,36	1,5	1,78
84172	РОСОЛЬКО	АНДРЕЙ	ВИКТОРОВИЧ	1,43	1,5	1,53
72223	БЫЧКОВА	ЕКАТЕРИНА	ВЛАДИМИРОВ	0,7	0,9	0,16
80231	ЛУПАШКО	ВАЛЕНТИН	ВАЛЕНТИНОВ	1,16	1,1	1,15
2815	КОВАЛЕНКО	ЕЛЕНА	ГЕННАДЬЕВНА	128	143,7	200
48318	ВИНИЧЕНКО	ВАЛЕНТИНА	ИВАНОВНА	94	114,6	83
2199	ВИНИЧЕНКО	СВЕТЛАНА	ВЛАДИМИРОВ	120	142,6	190
5721	ЖИТНИК	СЕРГЕЙ	ГРИГОРЬЕВИЧ	118	124,5	130
5657	ДЕЛЕЦ	ВАЛЕРИЙ	НИКОЛАЕВИЧ	252	240,8	250
5868	ЛЕЩИНСКАЯ	АННА	НИКОЛАЕВНА	275	309,8	390
6054	ПРОЦКО	АЛЕКСАНДР	ГРИГОРЬЕВИЧ	196	196,2	260
6067	ПРОЦКО	ПАВЕЛ	ГРИГОРЬЕВИЧ	130	119,1	170
8409	МОЙСЕЕНКО	ГРИГОРИЙ	СТЕПАНОВИЧ	115	114,1	160
8314	ЛАНЧЕНКО	НАТАЛЬЯ	ДМИТРИЕВНА	118	107,9	130
7888	ЛУТЧЕНКО	СВЕТЛАНА	ИВАНОВНА	129	115,8	120
8588	АНИСИМОВ	АЛЕКСАНДР	МИХАЙЛОВИЧ	338	340,1	410
8595	АНИСИМОВ	ЮРИЙ	МИХАЙЛОВИЧ	494	465,3	530
20369	ЦЕЛУЙКО	ЛЕОНИД	ФЕДОРОВИЧ	149	158,0	150
4267	БАЛОБАН	ВЛАДИМИР	ИВАНОВИЧ	80	77,7	130
20750	ГАЛУЗА	НАТАЛЬЯ	ВЛАДИМИРОВ	164	147,2	180
20757	ГАЛУЗА	ТАТЬЯНА	ВЛАДИМИРОВ	781	835,1	1200
129815	ЯЛЧЕНКО	ЕЛЕНА	БОРИСОВНА	251	251,4	290
129843	АКУЛИЧ	ИГОРЬ	ВАСИЛЬЕВИЧ	1076	1088,6	890

129489	САХАНЧУК	КОНСТАНТИН	НИКОЛАЕВИЧ	176	188,2	320
46746	КОПЕЛЕВА	ОЛЬГА	ВЛАДИМИРОВ	22	20,1	11
99634	КАЧАН	НАДЕЖДА	ПЕТРОВНА	50	149,1	120
98137	КАЛИНЧЕНКО	НАТАЛЬЯ	ВЛАДИМИРОВ	233	213,6	290
98140	ТИТОВА	ЛЮДМИЛА	ВЛАДИМИРОВ	162	162,8	220
99567	ГУША	ЕЛЕНА	НИКОЛАЕВНА	81	76,8	140
98655	ЖЕБИТ	ВАЛЕРИЙ	АЛЕКСАНДРОВ	258	274,5	290
98579	ДАШУК	ВАЛЕРИЙ	ВАСИЛЬЕВИЧ	493	477,2	510
98569	ДАНИЛЕНКО	ДЕНИС	ВИКТОРОВИЧ	270	304,5	280
98570	ДАНИЛЕНКО	ЛЮДМИЛА	ВИКТОРОВНА	126	128,1	120
98506	ВАСИЛЕНКО	СЕРГЕЙ	ЕВГЕНЬВИЧ	56	177,8	140
98424	АМЕЛЬЧЕНКО	НАТАЛЬЯ	АНАТОЛЬЕВН	159	386,3	350
98157	КОЖЕМЯКО	НИКОЛАВЙ	НИКОПАЕВИЧ	204	186,8	370
97823	ДЕНИСЮК	ИВАН	НИКОЛАЕВИЧ	383	387,9	430
97836	ДЕНИСЮК	СЕРГЕЙ	НИКОЛАЕВИЧ	889	938,7	1000
129911	ГОРОШКО	ГЕННАДИЙ	ВЛАДИМИРОВ	297	315,5	260
104098	РЕВЯКО	НАТАЛЬЯ	ИВАНОВНА	237	235,4	220
102544	ВАСИЛЬЕВ	АЛЕКСАНДР	НИКОЛАЕВИЧ	440	469,6	400
102547	ВАСИЛЬЕВА	МАРИНА	НИКОЛАЕВНА	417	469,7	390
101481	ИВАНЮТЕНКО	НАТАЛЬЯ	НИКОЛАЕВНА	337	329,6	340
129974	ЗАРЕНОК	МИХАИЛ	АНАТОЛЬЕВИЧ	247	227,0	200
165827	АНИЩЕНКО	ПАВЕЛ	ЛЕОНИЛОВИЧ	183	179,5	270
165908	ГЛУШУК	МАРИЯ	ПЕТРОВНА	192	202,9	270
166103	КОВАЛЬЧУК	АЛЕКСАНДР	НИКОЛАЕВИЧ	520	549,2	590
166269	МАКСИМЕНКО	НАТАЛЬЯ	АНДРЕЕВНА	400	422,4	390
166263	МАКСИМЕНКО	ГАЛИНА	АНДРЕЕВНА	220	248,1	220
203450	КАДЕТОВА	ТАТЬЯНА	МИХАЙЛОВНА	282	270,0	260
203557	РАЙКОВА	СВЕТЛАНА	ИВАНОВНА	384	343,6	400
203571	СПАСЕНОВ	ЛЕОНИД	ВЛАДИМИРОВ	384	343,6	400
155133	ЗУБЕЦ	АЛЕКСАНДР	НИКОЛАЕВИЧ	460	485,7	460
155265	КАШПЕРКО	ГАЛИНА	ВЯЧЕСЛАВОВН	667	750,4	670
157422	ВОДНИЦКАЯ	СВЕТЛАНА	СТАНИСЛАВО	303	285,8	280
154579	БОСЕНОК	АЛЕКСАНДР	АЛЕКСАНДРОВ	96	102,9	120
157170	ГОРЛЕНКО	ЕЛЕНА	АНАТОЛЬЕВН	1181	1328,8	1300
157175	ГОРЛЕНКО	ПЕТР	НИКОЛАЕВИЧ	291	283,5	290
196093	БОНДАРЕВ	ДМИТРИЙ	ВИКТОРОВИЧ	48	54,2	53
42906	ХНЫКОВ	ЮРИЙ	ВАСИЛЬЕВИЧ	10	10,9	11
8427	МОРДАСОВА	ОКСАНА	НИКОЛАЕВНА	110	117,6	200
152446	КУТАКОВ	СЕРГЕЙ	ДМИТРИЕВИЧ	115	115,6	120
147461	СОЛДАТЕНКО	ОЛЕГ	НИКОЛАЕВИЧ	89	89,0	95
131426	ШПАПАКОВ	ИВАН	МИХАЙЛОВИЧ	10	10,2	11
140104	ХРОМЧЕНКО	СЕРГЕЙ	АДАМОВИЧ	152	170,6	170
191901	СПИРАНЛЕЙ	МАРИЯ	НИКОЛАЕВНА	29	32,9	32
146761	МЕЛЬНИКОВА	СВЕТЛАНА	НИКОЛАЕВНА	62	65,5	38

25 November 1998

Prof. Nicolai Tronko, Director  
Institute of Endocrinology and Metabolism  
Vyshhorodska vul. 69  
Kyiv, 254114  
Ukraine

Dear Dr. Tronko:

It is time again for me to share with you impressions of our site visiting team. We did make individual comments during our plenary session and now I will try to summarize their statements which I received just now.

Even though overall, we were pleasantly impressed by the developing activities in the screening operations which, in spite of the summer months, managed to examine close to 600 candidates, there are a number of areas which concern us. I hope that these comments will be taken in constructive fashion because that is why they are made. The project is in its infancy in regard to practical screening operations and whatever needs to be modified or improved, can be done without damaging it.

We noted that the process of contacting subjects for screening appears to be largely in the hands of local medical facilities at the level of raion and below. Even though it seems advantageous to have the local people who know the subject to do this, there are also negative aspects to it: this arrangement gives your staff almost no feedback on the dynamics of the contacting process so that you miss the opportunity to learn first hand of some of the potential problems, such as: Why is the study unattractive to the subjects we want to reach? Which approach should be taken to improve the responsiveness?

It would seem desirable for the epidemiology staff to spend some time in the field observing the contacting process and have discussions with the medical personnel who are engaged in persuading the subjects to participate in screening examinations. Your staff should also conduct some post-screening interviews to learn the reaction of the subjects screened to the way in which they were handled in the process. We need to find out how the screening process might be improved. If there are unanswered questions, they must be attended to or the individuals will not return in the future.

We were especially concerned by the apparently low rate of response to the invitations for screening and believe this needs serious investigation. We are contemplating a possibility of

suggesting a formal, in-depth study of a representative subsample of subjects to learn all we can about the factors that may influence the response rate. A prominent US investigator is just finishing a psychological study of children and mothers in Ukraine and may be available to us in consultation.

In Belarus the address recovery rate is 73%. We have asked that they provide you with a list of address sources employed there for possible use in Ukraine, hoping that parallel organizations exist in Ukraine as well.

Partly because of this large problem but also because Dr. Derevianko can only give half time to the project, we think that the epidemiology staff needs to be strengthened and that additional training may be required. It would be centered on the recruitment of subjects for screening rather than on general epidemiological orientation. We will try to develop such a training in the U.S. if you have a suitable candidate.

As you know, efficient operation of the DCC is essential to the success of the project. We are greatly concerned about the stability of its technical staff. Mr. Kostin is the third head of the unit in several years and already there is a rumor that he may be leaving. Considerable amount of the software must be written without which the contacting and screening results will not be in the database and both you and we will be unable to study and report on our progress.

Dr. Markov's developing interest in quality assurance is a very encouraging sign. He seems to be working well with Dr. Mincey on the development of the necessary procedures and Dr. Tereshchenko recognizes their importance to the success of the project. Dr. Markov will need your support in gaining the acceptance and understanding of the staff.

The linkage workshop to be held next week should be an interesting and fruitful session for those attending. Dr. Howe will provide more specific information on linking various sources of available data which in turn may assist the staff in searching for cohort individuals.

Also, Dr. Howe has volunteered to re-calculate the power of the study on the basis of assumptions based on your experience thus far and his results may help us in determining the necessary size of the study and its logistic requirements, including the funding. He will need information that Dr. Derevianko and Mr. Kostin have promised to provide. It is obvious that the screening capacity will have to exceed 5,000 per year, as you have stated, if we hope to have sufficient information to evaluate the risk of thyroid cancer from I-131.

We welcome Dr. Likhtarev's overture to Dr. Howe with respect to a role in the eventual risk analyses. Hopefully their common interest may help to bring together the two essential parts of the study, dosimetry and risk analysis on the one hand, and the medical information on the other.

I would like to raise some concerns regarding the quarterly visits. I get mixed signals here. Should we continue the proven way by coming in larger groups about three-four times a year or would the recently tried approach of smaller groups designed for specific topics allowing

a more in-depth coverage and interaction of our teams with yours be more productive? Another option would be to try a mix of these modes. I would like to hear your thoughts on this so we can adjust our operations.

As you might have heard, there are some organizational changes coming up at NCI which, however, should not affect our project and our relationship adversely. When things settle down, I will report to you the outcome.

I am attaching a report of Dr. Bouville covering his impressions from his visit with the dosimetrists last month.

Sincerely yours,

Ihor J. Masnyk, Ph. D.  
U.S. Project Director

André Bouville  
Paul Voillequé  
8 February 1999

**COMMENTS ON THE REPORT ON IMPLEMENTATION OF MILESTONES  
OF THE 2<sup>nd</sup> QUARTER OF THE 3<sup>rd</sup> YEAR (SEP-NOV 1998) OF THE JOINT  
UKRAINIAN-AMERICAN SCIENTIFIC PROJECT:  
"STUDY OF THYROID CANCER AND OTHER THYROID DISEASE  
FOLLOWING THE CHORNOBYL ACCIDENT"**

(DOSIMETRY)

**GENERAL COMMENTS:**

The reports are of good quality. The information provided is very useful, and only limited additional information is requested.

**SPECIFIC COMMENTS:**

**Task 8.7:**

It would be useful to indicate: (1) whether all the questionnaires were filled in correctly (and, if not, what problems were encountered); and (2) whether all the responses are now available in computer form.

**Task 8.15:**

p.29, para.3 (continues on p.32): It would be useful to indicate the percentage of the total number of measurements with the SRP-68-01 that were performed in the 6 oblasts for which calibration results are shown in Figure 8.15.1.

Fig. 8.15.1: The axis label should be "Calibration Factor" as in the figure legend and the text. Although the figure is not incorrect, it would be preferable if the units in the figure were the same as those in the text ( $\mu\text{Ci h}$  per  $\mu\text{R}$ ).

Fig. 8.15.2: It appears that the dots on the figure represent results that are based on the SRP-68 measurements. That should be noted in the figure legend. The figure does show that there is better agreement between the average doses obtained by the two methods. However, there is no comparison of the distributions of estimates for each age group. It would be very helpful to add a table that shows the statistics of the two sets of dose estimates. The table should contain (for both the SRP-68-01 and NK-350 measurements) the number of estimates in each age group, the range of doses, the mean value, the standard deviation, and the median and geometric standard deviation (if appropriate).

p.33: It is not clear from the report whether the distribution of correction factors will be restricted to the local council (variation only over age groups) or whether the distribution

will include variations from one local council to another as well.

**Task 8.18:**

Table 8.18.2: Delete "Age groups" and the parentheses from the heading of the first column. "Years of birth" is the correct heading for its contents. Are the results for other birth years (1979-1985 and 1971-1974) similar?

**Last page:**

The planning chart for the 3rd quarter does not include a list of tasks for laboratory operations, DCC, pathology, or dosimetry.

Trip Report  
Visit to BelAm Thyroid Project Staff  
Minsk, Belarus  
20 October - 23 October, 1998

This was the first stop of a complicated visit to three locations. The American team members included the following NCI staff: Drs. G. Beebe and I. Masnyk; Columbia contract staff: Drs. G. Howe, R. McConnell, D. Fink, and E. Greenbaum; and the consultants: Drs. R. Brill, H. Mitchell and J. Robbins. The dosimetrists met a week before our arrival (Drs. A. Bouville and Voilleque). The Belarusian staff was represented by: Drs. Stezhko, Mrochek, Rzhetskiy, Lesnikova, Minenko, Buglova, Petrenko, Drozd, Danilova, Polanskaya

The first session pm 20 October began at 9 AM in the office of Dr. Mrochek, Director of the Institute and Deputy Director of the BelAm Project. Dr. Stezhko welcomed us and announced that initially we will work in small groups until the remainder of the team (Drs. Beebe, Mitchell and Fink) will arrive in Minsk. The first plenary session was planned for the next day. The proposed agenda is appended.

I conferred with Dr. Stezhko on various operational and administrative issues. The first was to explore the possibility of working through the International Science and Technology Center (ISTC) in providing money transfer for local support funds. Dr. Stezhko did not know much about this organization but liked the idea. Later, Dr. Mrochek expressed some worry that this may not be a legal procedure since payment in dollars is not permitted in Belarus. If this were possible they would like to pursue this approach. Still later, Dr. Stezhko identified the local representative of ISTC. Now we can begin to explore this approach through Dept of State channels. I expressed the need to straighten out the situation with equipment and supplies, to develop the inventory of received items and to develop lists of projected needs for consumable goods. Dates for the three meetings next year should be established: I proposed the following time frame: March-April; June-July and September-October.

Dr. Stezhko announced that Mr. Arthur Kuvshinnikov, who was the head of DCC, left the Institute and along with it the Project. The Minister of Health signed an order relieving him of his duties and assigned Dr. Nadia Lesnikova as the acting DCC head. Mr. Romanovski was hired to assist in the area of quality assurance activities. Then I discussed the report for the last quarter which we just received upon our arrival and pointed some inconsistencies, lack of clarity, some empty phrases that did not convey any information and suggested to have somebody take on the task of an overall review of the report before submitting it to us. Otherwise this just becomes a compilation of unrelated individual reports.

Next, I met with Dr. Petrenko to review the status of equipment and supplies for the

central laboratory. It seemed that majority of the required goods were already received or could be purchased on local market. What will be needed is to arrange for routine resupply of various hormonal test reagents. They are especially low on various antibodies.

The laboratory was transferred to a new facility on the outskirts of Minsk. It is under construction but Dr. Petrenko said that the work is going on. Later, while visiting this site, I found it practically unacceptable: no heat, holes in the walls where ducts are being installed, instruments under primitive plastic covers to protect them from dust, etc. I was "assured" that if the heat is not provided within a month, the laboratory will be relocated to a more acceptable site. This too is not a good solution as it would mean at least two more moves for the staff and all instrumentation.

An issue surfaced concerning analysis for ionized Ca. Drs. Fink, Mincey and the Ukrainian team in Kyiv maintain that the analysis can be done on processed and stored sera samples. Dr. Petrenko insists that analysis must be done on fresh material within 3-4 hours after collection. In addition, everybody but Dr. Petrenko feels that the instrument should not be moved around, especially on the rough roads throughout the country. Upon disconnecting the instrument the memory is erased and the unit must be reprogrammed each time. Disassembling the unit, packing it, unpacking and reassembling may result in breakages of some sensitive parts and requires re-calibration each time it is done, and the mobile teams work in weekly rotation. Dr. Petrenko was not persuaded and suggested that he should go to Kyiv to observe and discuss these aspects with Ukrainian workers. This was related to Dr. Stezhko and he tentatively agreed to such a trip.

During the period since our last visit, rumors have reached us that Mr. Kuvshinnikov might leave the project, and later he notified some of our consultants that he will quit towards the end of summer. This concerned several of us who worried that this could result in practical demise of the DCC operation and even of the project itself. When I raised our concerns, Dr. Stezhko provided the following explanation of what really has happened. He said that Mr. Kuvshinnikov was treated fairly and even favorably by him and Dr. Mrochek. Without a Ph.D. degree he was appointed chief of the laboratory in spite of the fact that people had difficulties working with him, not only those in different work groups but even within his own laboratory. He preferred to work alone, retaining close control of programs, passwords, and even keys so that others could not work in his absence. Only he could open many of the codes. Mr. Kuvshinnikov was offered assistance (a deputy slot was proposed to him) but he chose not to take this offer. When he presented his letter of resignation, Dr. Stezhko tried to talk him out of this move and then together with Dr. Mrochek kept this letter for a month without signing it to allow him to reconsider. Finally when by regulations he had to act, Dr. Mrochek signed the letter, the Minister of Health published an order relieving Mr. Kuvshinnikov of his position in DCC and appointing Dr. Lesnikova an acting chief.

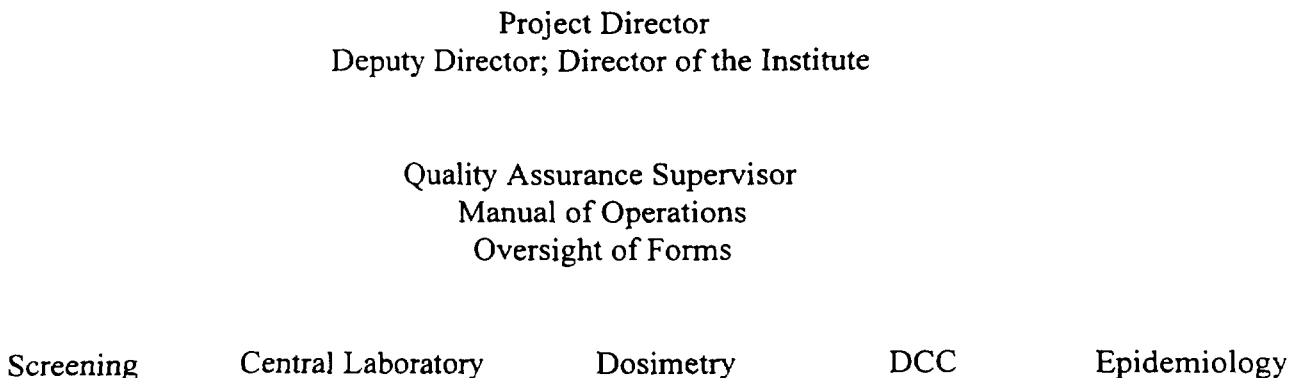
Dr. Mrochek felt that Mr. Kuvshinnikov was gambling on the total support by the American side, even against the decisions of project leadership. In spite of this, he was willing to

compromise and offered a part-time position to Mr. Kuvshinnikov, except that he could not come back full time to his old position as long as he remained outside the Institute. A chief consultant status could be given him, but Dr. Mrochek wondered whether it is really necessary. Dr. Lesnikova took over the duties and seems to be doing very well; there are no conflicts now among the staff.

Next day Dr. Polanskaya came to the Institute to discuss with Dr. Beebe, Dr. Stezhko and myself the possibility of her return to the project. She was offered a position in charge of the quality assurance and development of the manual of operations. She would be given assistance in these tasks. (Nota bene: Dr. Polanskaya did work on the project staff during the early formative years but then had to leave because of some conflict with the former director Dr. Stozharov).

Dr. Beebe felt that this position should be filled by a senior staff member, perhaps even at a level of a deputy so that appropriate authority would go clearly with it. Dr. Stezhko stated that in the past Dr. Mrochek was actually handling this activity in his role as Deputy Director of the project. He explained that individual team leaders would be responsible for development and revisions of various forms and Dr. Polenske would coordinate and oversee all this activity

I proposed a diagram for establishment of such a position:



Both Dr. Stezhko and Dr. Polanskaya agreed in principle with this diagram even though it is not exactly correct because some of the individuals working in these slots are not members of the Institute. Their affiliation however would be controlled by Ministerial Order.

Dr. Beebe elaborated on various levels of quality assurance: completeness of paper work, technical performance on all levels, the very process of the order of activities, timeliness, coordination etc. Then he posed the crucial question: is Dr. Polanskaaya interested in such a job?

Dr. Polanskaya noted that there will be little difference between the present proposal to her and her previous job in this project. She made an interesting observation that scientists try to standardize everything and clinicians tend to individualize their operations. It seems to be necessary to convert clinicians to scientists. Overall the approach to her new assignment is good

but practical aspects need to be elaborated: position, job description, salary, etc. Dr. Stezhko mentioned one possibility for her title as chief specialist which seemed to satisfy her, but she said that she will have to think about it some more.

During the next session with Dr. Stezhko he already had a chance to look into the situation with ISTC-Belarus branch (the parent organization is based in Moscow). An office exists in Sosny headed by Dr. Alexandr Borysovich Klepatskiy who is also Deputy Director of the Sosny Center; his telephone is 467 361). Dr. Stezhko reconfirmed their interest in working with this organization and will try to make an informal contact with them while we will work through the Department of State-Moscow loop.

In the meantime concern about the last money transfer was expressed. Evidently, there was a delay last time during the transfer between the New York based bank the Belarusian Bank. He asked to be notified as soon as we find out when the money was transferred, other wise valuable time is lost and everybody is anxiously waiting for this money.

The BelAm Oversight Group (equivalent to the American component of the Binational Advisory Group) met for the first time and approved continuation of the project but would like to see a conference organized on the effectiveness of the screening program. They feel a need to evaluate the benefit of this program to screened individuals.

Then we addressed the issue of mass-information, the need to have repetitive contacts with potential contacts, the use of non-scientific organizations, churches, local media in order to get through to the population at large. Obviously, this has not been practiced in Belarus and is a new experience to them. Dr. Stezhko seemed to accept this concept and will follow it up.

Considering the issue raised by Dr. Beebe about the level of contentment of various project members, especially the clinicians, Dr. Stezhko noted that there is some unrest in regard to the upcoming move and the teams would just like to get it over with so that they could start working in new facilities. They are satisfied with their work but would like to see the clinical evaluation to follow closely the screening process which at present is impossible due to the backlog in laboratory assays.

Thursday afternoon we visited the new facilities: some partially under construction, some a year away from completion, I think. The new location is on the outskirts of the city, about half an hour away from the center (by car). There is public transportation which ends practically at the door of the proposed new building where the screening, epidemiology and dosimetry units will be located. This used to be a hydro-therapy center (including mineral bath, curative mud treatments, etc.). It is still active with some 100 patients treated daily. The project units will be located in one wing, as yet not finished, the projected completion being some 2-3 months away. In general, the facility looks good in comparison to others we have seen here. It is a bit distant from center city, but reachable.

The proposed facility for the central laboratory and the DCC is a different story. This building is about one kilometer away from the proposed dispensary. It is an old machine construction factory which is being rejuvenated and totally overhauled. The single room in which the laboratory is presently located is not suitable even for storage. The building is dirty, unheated, with poor lighting, just like any other site under construction. Even when they complete the room or two or even the corridor, the rest of the building will still have to undergo additional refurbishing. I cannot imagine how they will be working in winter.

Obviously this is a shock even though we were being prepared for it. Dr. Rzhetskiy is optimistic that thing will work out and with his energy they just may. We need to reserve judgement until the spring visit but at this time it looks bleak. Dr. Stezhko tried to reassure me that should the construction fall behind the schedule, Dr. Petrenko will be moved to Dr. Rzhetskiy location.

#### Plenary Session.

Dr. Stezhko opened the session by reporting on the progress during the past quarter. Since the last visit considerable advances were made resulting to some extent from constructive criticism received from us. Cohort establishment proceeds satisfactory, various resources were searched for the candidates' current residences, regional registries were queried, individual passports, lists of evacuees, etc. An administrative file was created illustrating the searching process for cohort candidates. It became obvious that mobile teams will be needed to search for those that cannot come to Minsk. These teams will need to be equipped and some questions still exist on the processing of ultrasound data, on analysis of ionized Ca, on fine needle aspiration on the screening site, etc. Additional territory is anticipated for new coverage (Mogilev, Brest). The lists of the people living there has been lost but Moscow file should have them.

Last quarter 250 candidates were examined; from the beginning of the active screening 3313 candidates were seen. Some problems like non-availability of all hormonal tests, lack of the magneto-optical disks for the ultrasound seem to plague the screening operations. Because some of the hormonal assays could not be performed, processed blood samples were stored frozen. There is presently a back-log of some 1,500 specimens. (Nota bene: although the supply situation leaves something to be desired, the laboratory was inactive for 2-3 months also because of the move to new facilities and because the Abbott IMX instrument was broken; it was repaired just 2-3 weeks before our arrival).

Dosimetrists interviewed 249 individuals. They received all the ordered equipment for field work. Two papers have been drafted and questionnaires have been prepared for possible estimates of the doses from medical irradiation.

The staff worked on operations manuals and on instructions of how to fill out various forms. Work continued on quality assurance manuals: each group prepared sections on their activities. It would be helpful to them to obtain some western literature on this subject and

perhaps a workshop could be organized for all staff members to familiarize them adequately with quality assurance concepts.

In the discussion that followed, Dr. Beebe insisted on the need to pay serious attention to cohort selection and to invitations for screening. The source of Dr. Rzhetskiy screening should not dry out. Epidemiology and DCC staff did remarkable work up to now in finding addresses but the non-response rate is very high. A good record of what is achieved by mobile teams should be kept. Will they solve the problem by themselves or should other ways be looked for? The contact with Japanese in Gomel must be maintained and there is an obvious need for another fixed screening site, possibly in Gomel.

Dr. Howe was impressed with efforts made in tracing subjects (presently at 70%). It would be difficult to do this in the USA. The problem here is clearly the non-responsiveness of people. We have to be constantly alert to the possibility of introduction of bias if any modifications are made in the cohort. He offered to recalculate the statistical power on the basis of the data available now. To reach more individuals mobile teams and a stationary Gomel center would be important. If 15 K subjects are to be screened, the target population should be larger than 15 K. He tested his record linkage program on BelAm computers and it works. Hence this technique may be helpful in the near future.

Dr. Stezhko noted that up to now the first selection was used in trying to reach the screening candidates. Mobile teams will be sent to reach those that fail to show up. Concerning Gomel, three years ago there was one approach considered, now they feel differently; at first a mobile team size unit should be placed in Gomel without the full contingent of all operational groups. They should work similarly to the Ukrainian methods using primarily mobile teams.

Dr. Minenko felt that all of high dose people (8,000) should be included in the cohort (only 4,000 are now, and only 25 have responded). He wondered whether they should go for all 8,000 or can they add high doses from the calculated or "passport" values?

Dr. Howe thought that if 6,000 could be actually screened, then the power would be OK. New linkage program may add new contacts. Effort must be made to get them to screening once the addresses will be found.

Dr. Mitchell was pleased with data management. Quality assurance work on data introduced is still not here. We still modify the forms. The programming effort must be directed towards automatic feed-back for quality of their input.

Dr. Robbins stressed the need to develop criteria for patient referral for clinical work-up and for fine needle biopsy. He noted that there are no more children under 12 years of age which should simplify the operations somewhat. He reviewed some screening records and even though there are some problems, they are not serious. More frequent meetings among the clinicians should be held to discuss their experiences. We are being careful to modify forms and to do it

only if that is necessary. But the pathology and the cytology forms were the last to be developed and still need some work.

Dr. McConnell agreed that the decision for fine needle aspiration of nodules less than 1 cm in size should be made on strictly ultrasound criteria to avoid bias. The summary form should be changed to reflect WHO criteria. Uniform coding must be adhered to to facilitate data entry and subsequent analysis. He met with Dr. Demidchik in an attempt to improve cooperation between endocrinologists and surgeons.

Dr. Greenbaum worked with cytologists. She was happy to note that the new facilities will permit the ultrasonographers and cytologists to work together in close proximity.

Dr. Brill noted some problems in ultrasound image recording system, He will try to get replacement parts and he noticed that the recently received machine does not have it. He saw the 3D equipment in Aksakhovschina and thought it would be nice to do a study comparing various detection modes with surgical results; this type of work could find grant support.

Dr. Fink stated that the laboratory work need to be completed within a week of screening. The back log should be caught up with as soon as possible. Any abnormal results obtained in the laboratory should be reported to clinicians. Finally he was happy to see that Dr. Petrenko began implementing new techniques of quality assurance. Dr. Fink would like to run a comparative analysis between his laboratory and Dr. Petrenko's. The ionized Ca analysis controversy needs to be resolved quickly.

Drs. Beebe, Howe and Rzhetskiy found a rare point of agreement the need for more advertising of the program to bring more responders.

Dr. Drozd noted that in Gomel over 2,000 children were already examined (Japanese program?) and most of them are from our cohort. We should start getting serious in reaching them.

February 24, 1999

### Draft Material on Present Status of Project in Ukraine

**The Cohort** In late 1996 and early 1996 Dr Likhtaryev provided Dr Tronko with his file of about 100,000 children with acceptable direct thyroid radioactivity measurements in 1986. Those measured in the raions specified in the protocol as the area of operation for the study numbered about 65,000 and their estimated dose distribution compares as follows with the protocol specification and the initial selection for the study cohort:

	Protocol	Measurement File	Initial Selection
1 or more Gy	10,900	9,500	9,500
0.3-.99 Gy	19,300	17,200	5,000
<0.3 Gy	20,000	38,500	5,000
Total	50,200	65,200	19,500

As with the Moscow file, there were important gaps in elements of identification, especially with respect to the patronymic and the day and month of birth. All had place of examination, surname, and year of birth.

**Addresses and Response to Invitations to Screening** Addresses were sought initially from the files of the Institute itself and from the Chernobyl Registry. Because these results were disappointing lists were sent to the main polyclinics in the raions where the measurements had been made and the lists were hand-posted with current addresses or other information as available. An address has been found for about 70 percent but known errors would reduce this number to about 60 percent. Major address sources have not yet been tapped, but access is being sought to such files as that of the Ministry of Internal Affairs that tracks all individuals as they come of age for military service. The rate of response to the invitation to screening is running about 50 percent, but is about 70 percent for those resident in Kiev where telephone access is available.

As noted in the report for Belarus, consideration is being given to incentives, with some preference at NCI for a cash reimbursement for transportation, loss of working time, etc. In Kiev the discussion of incentives has centered on vitamins. The cash amount under discussion at NCI is the equivalent of \$5, but this has yet to be discussed with Dr Tronko. Also, an in-depth survey of attitudes, perceptions, and level of information is under preliminary discussion with a well-established survey group in Kiev.

Examinations began in April, 1998, and thus far about 1,900 have been screened, principally by mobile teams in the field, with 3 new cases of thyroid cancer diagnosed by mid-February. The desirability of a second fixed screening center was under discussion. The Ministry of Health is very supportive of the project and projects its influence into the field, especially through requiring assistance from health facilities at the raion level.

**Current Problems** A quality control officer has recently been appointed to coordinate QC efforts and to teach and demonstrate QC methods. Although publicity has included both radio and newspapers, the success of contacting remains low and the process, which is partly dependent on the efforts of uncompensated personnel at the raion level, is not producing the information needed to plan improvements. The recording and storage of ultrasound images do not meet protocol requirements and the ultrasound equipment being taken into the field is too heavy and hard to move. The referral policy for fine-needle aspiration biopsy and for surgery is not standardized and also needs coordination with the practice in Belarus. Partly because an adequate supply of computers did not arrive until the summer of 1998, there is a lag in the availability of software for entering into the database information developed by screening. Provision is only now being made for a continuous supply of supplies. The operations manual, based largely on that developed in Belarus, needs to be updated to reflect current practice. Finally, the US AID has funded a US contractor to examine children in UA for thyroid cancer and for psychological problems in some areas where Dr Tronko's mobile teams will be operating. Coordination has been discussed but at best will be imperfect because the AID group is not drawing blood for thyroid hormone tests.

February 23, 1999

### Draft Material on Present Status of Project in Belarus

**The Cohort** In 1996 the Moscow dosimetry group provided a file of 39,000 with acceptable 1986 direct thyroid measurements and beginning in early 1997 selections were made for the cohort, as follows:

Estimated Dose Range, Gy	Original File	First Two Selections
1 or more Gy	8,400	8,400
0.3 - 0.99	11,000	6,800
<0.3	19,700	4,500
Total	39,100	19,700

For the first selection of 15,000, addresses have been sought from a wide variety of sources, including the Chernobyl Registry. The second selection is new and no data are as yet available. There are major difficulties with the ID on the Moscow file, especially in regard to specific address in 1986, completeness of name, and completeness of date of birth.

**Addresses and Response to Invitations to Screening** As of 10/98, work on the first selection of 15,000 could be summarized as follows, by dose group:

	8,400 high dose	7,000 lower dose
Address reported	68 %	78 %
No response to invitation	55 %	43 %
Wrong address	10 %	14 %
Answered invitation	27 %	37 %
Screened/answered	60 %	59 %

Consideration is being given to the issue of incentives, with some preference for a cash reimbursement for transportation, loss of working time, etc. The amount under discussion at NCI is the equivalent of \$5, but this has yet to be discussed with the director of the project in Belarus, Dr Stezhko. Also, the concept of an in-depth survey of attitudes, perceptions, and information levels is being explored with an experienced survey group in Kiev; it is believed that the findings in Ukraine would be similar to those in Belarus.

At that time 2,100 had been screened, mainly by the Dispensary in Minsk. Subsequently considerable use has been made of a mobile team examining subjects in the Gomel Oblast south of Minsk, and the reported total of first examinations in mid-February was 3,508 among whom 13 thyroid cancers were diagnosed for the first time, and 28 subjects had previously been diagnosed with thyroid cancer, or 41 cases in all.

**Second Center in Gomel City** The protocol assumes that a second fixed enter will be established in the city of Gomel in the oblast of that name that suffered the worst fallout. Preliminary discussions on the establishment of the center in Gomel are scheduled for the second quarter of calendar 1999, with a decision to be reached in the third quarter. The location of

subjects in the cohort extends to all parts of Belarus and subjects in the Gomel Oblast are currently being examined by a mobile team sent from Minsk.

**Current Problems** Although the screening has been going well for those with good addresses and apparent interest, there is a large backlog of unexamined bloods that arose during a period when kits were lacking, and the database for the clinical data from the 1997 screening is also incomplete. Responsibility for quality control has passed through several hands but is now being approached in a very determined way. Very unsettling at the moment is the necessity for the Institute to move to other quarters, some of which are not yet ready. The Minsk dispensary has also had to move to less desirable quarters, but that move has been completed. The condition of the building earmarked for the Data Coordinating Center and the Epidemiology Group made a poor impression on the visiting team in October. Instability of high-level officials has been a chronic problem: three Ministers of Health, four directors of the Institute of Radiation Medicine and Endocrinology, and the ousting of the chief endocrinologist of the Institute with whom the protocol was planned.

2/25/99

## Summary of Proposed Changes to the UkrAm Thyroid Study Protocol

### Cover Page

The list of names of U.S. and Ukrainian Committees is out of date. Should it be left for what it was when the protocol was written or brought up to date?

What about dating? Should the original date be left or the eventual date of approval by the Bi-national Advisory Group be inserted at that time?

### Section 3.1.2.4.

Add the following text at the end of paragraph 2:

“Efforts should be made to collect in an electronic database all the reliable information released to the deposition of the ground and on the environmental concentrations of I-131 for the territory of Ukraine”

### Section 3.1.4.2.

In paragraph 1, lines 7-10 delete the sentence:

“Thus, a pilot study.....to the end of.....Radiation measurements.”

In its place substitute the text:

“A pilot study on the utility of contemporary measurements of I-129 in soil is in progress in Belarus. If this pilot study provides encouraging results for the prospect of decreasing the uncertainty in calculated thyroid doses, a measurement program of I-129 in Ukrainian soils will be undertaken.”

### Section 3.3.

The fixed medical centers in Ukraine need to be redefined.

### Table 3.3.1.

Eliminate the old classification of goiter size, substitute the new WHO classification:

Grade 0 = no goiter (that is, no thyroid enlargement)

Grade 1 = thyroid enlarged but not visible with neck in normal position

Grade 3 = thyroid enlarged and visible with neck in normal position

### Section 3.3.3.

Eliminate the sentence in lines 9-11 “If free T-4.....to the first year” and replace with text:

“Hypothyroidism to be ascertained by serum TSH on every visit, with Free T4 or T4 done whenever the TSH is abnormally high or low.”

### Section 3.3.4.

Eliminate the entire text of this paragraph; substitute the following:

“Iodine nutrition to be ascertained by measuring urine iodine content of a random urine sample on every subject at the first visit. This will perhaps be repeated at a time to be decided at

measured, and samples will not be sent to the University of Massachusetts for verification.”

Section 3.3.5

In line 2, delete the text after (Anti-TPO): at 1 or 2 year intervals and substitute: “anti-TPO to be done on every visit, followed by anti-Tg, if positive.”

Section 3.3.6

Delete the entire text and substitute:

“Hyperthyroidism to be ascertained by serum ionized calcium on every visit. When elevated, PTH immunoassay will be done in a reference laboratory.”

Section 3.3.7

Delete the second sentence starting with: “Selected duplicate...” to the end of paragraph.

Section 3.4.2

Under “o Tests performed : eliminate T-4, T-3 and Albumin

Section 4.1.6

Delete.

Section 4.4.2

Delete the last sentence in the paragraph substituting the text:

“Procedural changes, new equipment will require overlap time during which duplicate tests will be run to assure reproducibility.

Section 4.4.3

Delete the entire text, substituting:

“Serum assays will be performed in single determinations.”

Section 4.4.5

Delete the second sentence in its entirety.

Section 4.5.2

Delete the text “at least 4 times a year”, substituting:

“The U.S. consultant, based on most recent experience, will determine the frequency of reviews; 4 reviews per year may not be required.”

Section 5.3.1

Delete.

Section 5.3.2

Delete the old text, substituting:

“Each ultrasound system will have an image digitizer (Camtronics Magneto Optical Disk

Delete the old text, substituting:

“Each ultrasound system will have an image digitizer (Camtronics Magneto Optical Disk {MOD} recorder). A standardized set of images will be recorded for each patient in whom normal findings are noted, and extra images will be recorded when abnormalities are found.”

### Section 5.3.3.

Add the following text under this new section:

“Ultrasound images recorded on MOD disks will be backed up on DAT tapes at the DCC. Peripherals on the DCC system will include a DAT tape, MOD read/write device, and a R/W CDROM along with the other standard devices specified elsewhere. The DCC will transfer image data from the MOD disks to DAT tapes for long term archiving at a safe remote place, and will rewrite images onto CDROM disks in a format suitable for review on standard PCS located at or near the Ultrasound clinical units.”

### Section 7.

Delete the text starting with line 6: “Resource requirements”...and ending with “Center for Radiation Medicine.”

### Section 7.1.

Delete sections 7.1; 7.1.1; 7.1.2; 7.1.3; 7.1.4

### Section 7.2.

Delete in its entirety

### Section 7.3.

Delete in its entirety

### Section 7.4

Add at the end of paragraph 2:

“(c) Local assistance needed to supplement the salary of the Ukrainian personnel working on the study.”

### Section 7.5.

Delete the heading 7.5.1;

In the UKRAINIAN BUDGET paragraph: second line substitute “salaries of” for “paying”; delete in lines 3-5 the text: “purchase of such equipment and materials which are not stipulated in the protocol as a U.S. responsibility;”

In the U.S. BUDGET paragraph: delete entire text after the end of the first sentence. Add the following text: The budget will be reviewed annually and proposed to NCI leadership in the established process. U.S. will provide approved equipment and supplies and negotiated local support funds for the Ukrainian project, for possible expansion of additional screening centers and mobile teams, training support for approved staff as well as funds to remunerate the study participants for their travel to the screening center. In U.S. the budget will include expenses for

## Section 10.2

Rewritten text is attached.

### 10. Project Management

#### 10.1 Binational Advisory Group

Ukrainian and NCI authorities will be assisted by a Bi-National Advisory Group consisting of 10 members, five to be named by Ukrainian Ministry of Health and five by the U.S. National Cancer Institute (after consultation with other U.S. sponsoring agencies). Nominations should reflect the well-established reputation of each candidate from the following areas of expertise: endocrinology, radiation biology, radiation dosimetry, radiation epidemiology and clinical sciences/pathology. Following its establishment the Advisory Group will be self-perpetuating body selecting future members from among those nominated by the sponsoring agencies and by its own membership.

Members of the Bi-National Advisory Group will serve five-year terms except that, initially, in order to provide reasonable continuity, the candidates will be appointed for three-, four-, five-, six-, and seven-year terms from each national authority. Members may not serve more than two terms. Project staff may not serve as members of the Advisory Group. Former staff members should observe a two-three years hiatus from any involvement in project operations.

The Advisory Group will select its own co-chairmen, one Ukrainian and one American (the latter would have been already selected by American membership as the Chairman of the American moiety). The Bi-National Advisory Group will meet at least once a year in Ukraine. It may hold other meetings when necessary or upon request from either the Ukrainian or the U.S. Project Director. The co-chairmen will jointly administer the activities of the Advisory Group including such matters as the agenda, number of meetings each year, alternation of chairmanship, etc.

The Advisory Group will respond to requests for advice from the Ukrainian and American Project Directors and will initiate its own agenda topics and investigations. It will be responsible for (1) recommendation of changes in the governing research protocol based on suggestions made to it by either the Ukrainian or the U.S. Project Director, or on its own observation, (2) review of budgets presented by the Ukrainian and U.S. Project Directors, (3) review of the progress of the work on the basis of official reports; e.g., the quarterly reports of the Ukrainian Project Director, information presented at its meetings, reports of site-visits, and its own investigations, and (4) advice on publication policy. With the approval of the co-chairmen, data created by project activities will be made available to individual Advisory Group members for informational and review purposes. The Advisory Group will determine its own agenda and operating rules, including the rotation order of individual members; the Group has the right to close the meetings to convene in executive sessions. The Ukrainian Project Director will provide secretarial and other logistical support for the Group's meetings and activities in

Ukraine and the U.S. Project Director for meetings in the U.S. The official communication language will be in English. The Project Directors shall be responsible for providing competent translations and interpreters.

### 10.2 Management

The Project Directors will be responsible for scientific activities (e.g., clinical, laboratory, dosimetric, and epidemiologic), for administration (e.g., personnel, data management, training, fiscal matters, allocation of resources), for preparation of required reports, communication with the press and with various entities of the governments. In their respective areas, they will be responsible for logistic support for the Bi-National Advisory Group. Reallocation of supplies and equipment provided by the U.S. Government will require consent of the U.S. side. One of the crucial tasks for the Ukrainian Project Director is the appointment of a Quality Assurance Officer.

### APPENDICES

Delete Appendices A and B; update American Organizational chart to be added to Appendix C.

2/25/99

## Summary of Proposed Changes to the BelAm Thyroid Study Protocol

### Cover Page

The list of names of U.S. and Belarus Committees is out of date. Should it be left for what it was when the protocol was written or brought up to date?

What about dating? Should the original date be left or the eventual date of approval by the Bi-national Advisory Group be inserted at that time?

### Thyroid Dosimetry

Insert a list of publications which appeared since the protocol was written.

The list is appended.

### Section 3.1.1.1.

Add the following text at the end of paragraph 2:

"In addition, about 30,000 direct thyroid measurements were conducted in the Brest region. As a relatively large number of thyroid cancers has been observed in that region, it could be envisaged to add the results of these measurements to the dosimetry data bank. Unfortunately, it is not clear whether the identification of the children who were measured can be found."

### Section 3.1.2.4

Add the following text at the end of paragraph 2:

"Efforts should be made to collect in an electronic database all the reliable information released to the deposition on the ground and on the environmental concentrations of I-131 for the territory of Belarus."

Delete in paragraph 5 the text:

"on the environmental concentrations of I-131."

### Section 3.1.4.2.

Delete the last sentence: *of paragraph 1*

"Thus, a pilot study.....to the end of.....Radiation measurements."

### Table 3.3.1.

Eliminate the old classification of goiter size, substitute the new WHO classification:

Grade 0 = no goiter (that is, no thyroid enlargement)

Grade 1 = thyroid enlarged but not visible with neck in normal position

Grade 2 = thyroid enlarged and visible with neck in normal position

### Section 3.3.3.

Eliminate first sentence. Substitute text:

"Hypothyroidism to be ascertained by serum TSH on every visit, with Free T4 or T4 done whenever the TSH is abnormally high or low."

### Section 3.3.4

Eliminate the entire text of this paragraph; substitute the following:

"Iodine nutrition to be ascertained by measuring urine iodine content of a random urine sample on every subject at the first visit. This will perhaps be repeated at a time to be decided at

a later date. In particular, sampling of a subset of subjects based on geographical distribution will not be done, 24-hour urine collections will not be done, urine creatinine will not be measured, and samples will not be sent to the University of Massachusetts for verification."

#### Section 3.3.5

In line 2, delete the text after (Anti-TPO): at 1 or 2 year intervals and substitute: "anti-TPO to be done on every visit, followed by anti-Tg, if positive."

#### Section 3.3.6

Delete the entire text and substitute:

"Hypothyroidism to be ascertained by serum ionized calcium on every visit. When elevated, PTH immunoassay will be done in a reference laboratory."

#### Section 3.3.7

Delete the second sentence starting with: "Selected duplicate..." to the end of paragraph. Add the text: "With increasing future workload, it may be necessary to open a second laboratory."

#### Section 3.4.2

Under "o Tests performed : eliminate T-4, T-3 and Albumin

#### Section 4.1.6

Delete.

#### Section 4.4.2

Delete the last sentence in the paragraph substituting the text:

"Procedural changes, new equipment will require overlap time during which duplicate tests will be run to assure reproducibility.

#### Section 4.4.3

Delete the entire text, substituting:

"Serum assays will be performed in single determinations."

#### Section 4.4.5

Delete the second sentence in its entirety.

#### Section 4.5.2

Delete the text "at least 4 times a year", substituting:

"The U.S. consultant, based on most recent experience, will determine the frequency of reviews; 4 reviews per year may not be required."

#### Section 5.3.1

Delete.

#### Section 5.3.2

Delete the old text, substituting:

"Each ultrasound system will have an image digitizer (Camtronics Magneto Optical Disk {MOD} recorder). A standardized set of images will be recorded for each patient in whom normal findings are noted, and extra images will be recorded when abnormalities are found."

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Delete the old text, substituting:

"Ultrasound images recorded on MOD disks will be backed up on DAT tapes at the DCC. Peripherals on the DCC system will include a DAT tape, MOD read/write device, and a R/W CDROM along with the other standard devices specified elsewhere. The DCC will transfer

image data from the MOD disks to DAT tapes for long term archiving at a safe remote place, and will rewrite images onto CDROM disks in a format suitable for review on standard PCS located at or near the Ultrasound clinical units.”

Section 5.3.4

Delete

Section 5.3.5

Delete

Section 7

Delete the text starting with line 5: “ Resource requirements.....up to the end of this section ending with .....the Oncology Center.”

Section 7.1

Delete sections 7.1; 7.1.1; 7.1.2; 7.1.3; 7.1.4

Section 7.2

Delete in its entirety

Section 7.3

Delete in its entirety

Section 7.4

Add at the end of paragraph 2:

“(c) Local assistance needed to supplement the salary of the Belarusian personnel working on the study.”

Section 7.5

Delete the heading 7.5.1;

In the BELARUSIAN BUDGET paragraph: second line substitute “salaries of “for “paying”; delete in lines 3-5 the text: “purchase of such equipment and materials which are not stipulated in the protocol as a U.S. responsibility;”

In the U.S. BUDGET paragraph: delete entire text after the end of the first sentence. Add the following text: The budget will be reviewed annually and proposed to NCI leadership in the established process. U.S. will provide approved equipment and supplies and negotiated local support funds for the Belarusian project, for possible expansion of additional screening centers and mobile teams, training support for approved staff as well as funds to remunerate the study participants for their travel to the screening center. In U.S. the budget will include expenses for the travel for consultants, funds for the support contract, support to members of the Binational Advisory Group and funds for approved meeting travel for the purpose of reporting study data.

Delete section 7.5.2.

Section 10.1

Rewritten text is attached.

Section 10.2

Rewritten text is attached.

APPENDICES:

Delete appendices A, B, C, and update appendix D.

## 10. Project Management

### 10.1 Binational Advisory Group

Belarusian and NCI authorities will be assisted by a Bi-National Advisory Group consisting of 10 members, five to be named by Belarusian Ministry of Health and five by the U.S. National Cancer Institute (after consultation with other U.S. sponsoring agencies). Nominations should reflect the well-established reputation of each candidate from the following areas of expertise: endocrinology, radiation biology, radiation dosimetry, radiation epidemiology and clinical sciences/pathology. Following its establishment the Advisory Group will be self-perpetuating body selecting future members from among those nominated by the sponsoring agencies and by its own membership.

Members of the Bi-National Oversight Group will serve five-year terms except that, initially in order to provide reasonable continuity, the candidates will be appointed for three-, four-, five-, six-, and seven-year terms from each national authority. Members may not serve more than two terms. Project staff may not serve as members of the Advisory Group. Former staff members should observe a two-three years hiatus from any involvement in project operations.

The Advisory Group will select its own co-chairmen, one Belarusian and one American (the latter would have been already selected by American membership as the Chairman of the American moiety). The Bi-National Advisory Group will meet at least once a year in Belarus. It may hold other meetings when necessary or upon request from either the Belarusian or U.S. Project Director. The co-chairmen will jointly administer the activities of the Advisory Group including such matters as the agenda, number of meetings each year, alternation of chairmanship, etc.

The Advisory Group will respond to requests for advice from the Belarusian and American Project Directors and will initiate its own agenda topics and investigations. It will be responsible for (1) recommendations of changes in the governing research protocol based on suggestions made to it by either the Belarusian or the U.S. Project Director, or on its own observation, (2) review of budgets presented by the Belarusian and U.S. Project Directors, (3) review of the progress of the work on the basis of official reports; e.g., the quarterly reports of the Belarusian Project Director, information presented at its meetings, reports of site-visits, and its own investigations, and (4) advice on publication policy. With the approval of the co-chairmen, data created by project activities will be made available to individual Advisory Group members for informational and review purposes. The Advisory Group will determine its own agenda and operating rules, including the rotation order of individual members; the Group has the right to close the meetings to convene in executive sessions. The Belarusian Project Director will provide secretarial and other logistical support for the Group's meetings and activities in Belarus and the U.S. Project Director for meetings in the U.S. The official communication language will be in English. The Project Directors shall be responsible for providing competent

translations and interpreters.

## 10.2 Management

The Project Directors will be responsible for scientific activities (e.g., clinical, laboratory, dosimetric, and epidemiologic), for administration (e.g., personnel, data management, training, fiscal matters, allocation of resources), for preparation of required reports, and for communication with the press and with various entities of the governments. In their respective areas, they will be responsible for logistic support for the Bi-National Advisory Group. Reallocation of supplies and equipment provided by the U.S. Government will require consent of the U.S. side. One of the crucial tasks for the Belarusian Project Director is the appointment of a Quality Assurance Officer.

On the 26 April 1986 in the early morning hours the IV reactor at the Chornobyl Nuclear Power Plant exploded spreading radiation principally throughout Belarus and Ukraine. It took several days for this event to be reported by Swedish monitoring stations and even longer to be acknowledged by the Soviet authorities. In the meantime chaos dominated over the activities around Chornobyl, Prypiat, the Nuclear Plant and the surrounding areas where the plant staff and firefighters were trying to control what they thought to be just a fire.

The feverish activity following realization that a nuclear accident has occurred accompanied by mobilization of massive forces attempting to do their best in controlling this accident, the evacuation of thousands of residents, hasty measurement of their accumulated doses, recording all these data in a hurry resulted in current difficulties we face working on the Chornobyl projects, especially in identifying and locating individuals selected and verifying their recorded doses.

To add to this, all through the 1986 and 1987 Soviet Union actually refused the offers of assistance from US Agencies and even from National Academy of Sciences. In their view this was not a Public Health problem but an issue of concern only to Nuclear Energy Authorities.

In 1987 President Ronald Reagan suggested that the US and USSR cooperate in the field of civilian nuclear reactor safety. Then in 1998 Chairman Gorbachev accepted his suggestion and an agreement to cooperate in research covering among other activities the environmental and health issues resulting from Chornobyl accident was signed by the Nuclear Regulatory Commission on the U.S. side and the USSR State Committee for the Utilization of Atomic Energy. This activity was under the umbrella Agreement for Peaceful Uses of Atomic Energy and the Implementing entity was the Joint Coordinating Committee on Civilian Nuclear Reactor safety. Later, in 1989 NRC turned to DOE requesting them to assume the responsibility for environmental and health issues. This followed by the first meeting of US and Soviet experts in September 1989 to assess cooperative research possibilities, still within the Soviet Union. As a result of this meeting, where for the first time NCI staff was represented (Drs. A. Bouville, R. Miller and G. Beebe), a number of potential research projects was generated, among them the long term prospective study of thyroid cancer among the exposed children and leukemia among the liquidators. In 1990 DOE requested that NCI take over the responsibility for developing and implementing such studies with the Soviet counterparts. NCI established two ad hoc working groups for both projects with membership consisting of prominent scientists, experts in radiation biology and dosimetry, in dose reconstruction, endocrinology, nuclear medicine, hematology, in laboratory techniques, cytogenetics, epidemiology, statistics, computer sciences and in data management.

#### The thyroid working group

David V. Becker, M.D., Chair  
Lynn R. Anspaugh, Ph.D.  
Gilbert W. Beebe, Ph.D.  
Andre Bouville, Ph. D  
A. Bertrand Brill, M.D., Ph.D.  
Jacob Robbins, M.D.  
Roy E. Shore, M.D., Dr. P.H.  
Lester VanMiddlesworth, M.D.,  
Bruce W. Wachholz, Ph.D.  
Jan Wolff, M.D., Ph.D.

#### Leukemia working group

Gilbert W. Beebe, Ph.D., Chair  
Lynn R. Anspaugh, Ph.D.  
John D. Boyce, Jr., Sc. D.  
Andre Bouville, Ph.D.  
Scott Davis, Ph.D.  
Geoffrey R. Howe, Ph.D.  
Ronald Jensen, Ph.D.  
L. Gayle Littlefield, Ph.D.  
Ian Magrath, M. B.  
Leslie Robinson, Ph. D.  
Bruce W. Wachholz, Ph. D.

In November 1990 they attended the WHO conference in Chernyiv, Ukraine where the first contacts were made with the Ukrainians who made certain proposals which at that time appeared to be beyond the scope of potential U.S. cooperation.

Some six months later USSR ceased to exist and then two newly independent countries Belarus and Ukraine required now separate approaches because of different government policies, new individuals among the leadership in medical-scientific arena and different organizational schema. A new round of talks and negotiations for continued cooperation under new country-specific conditions led eventually to three projects: one each with Ukraine and Belarus on the effects of Chornobyl accident on thyroid cancer among children; and one project in Ukraine on leukemia/lymphoma among the liquidators of the effects of this accident.

Although initially the project costs were to be underwritten by DOE, in 1992 DOE invited NCI to share in financing the operational expenses (primarily for NCI personnel), in development of the protocols, training foreign nationals, travel, etc. NCI agreed to match the DOE funding, which at that time was \$250,000.00 each. This level was never even approached until FY 1997.

The early discussions with Belarusian and Ukrainian counterparts made it clear that, in order to be successful, these projects need to be supplied with modern equipment, reagents and miscellaneous supplies. NRC contributed US \$1 Million to be shared between Ukraine and Belarus thyroid projects and later the French Institute of Nuclear Safety and Protection donated \$250,000.00 for the leukemia project. Initially, NCI was not ready to handle procurement of equipment and supplies and DOE took over this responsibility and handled it through a contractual agreement.

Finally in 1992, six years post Chornobyl we were ready to begin serious work on development of protocols for the thyroid projects in Belarus and Ukraine. In 1994 an agreement

was reached with Belarus and signed in an official ceremony by Belarus and U.S. government representatives and in 1995 a similar agreement was signed in Ukraine.

Late in 1996 this process was repeated for leukemia, however with the difference that, before entering a full fledged long term study, a feasibility phase was to be carried out to clear the way for a long term commitment and to answer troubling questions concerning its practicality.

In the early period (starting in 1994 for Belarus and 1995 for Ukraine) NCI carried out the scientific management of these projects while DOE maintained the financial responsibilities for the equipment and supplies and for local support. In December 1996 a new Interagency Agreement was signed between DOE and NCI in which all management and scientific responsibilities for these studies were transferred to NCI and then an Interagency Agreement was arranged between NCI and Veterans Affairs National Acquisition Center (VANAC) in Niles, IL to provide procurement and shipping services to the three projects. During the past year this organization was able to process orders for close to one million dollars worth of goods, enabling us finally to implement practical screening operations in the thyroid projects.

Until 1996 the NCI staff consisted of four professionals and 1½ clerical support. With the expansion of the responsibilities for scientific and managerial activities, a need arose for additional staff or a support contract. Late in FY 1997, after an open competition, the Columbia University became our partner in these projects with Dr. Geoffrey Howe as the principal investigator.

During the early phase (1994-1997 in Belarus and 1995-1998 in Ukraine) our concern was primarily to provide the necessary equipment and supplies, develop organizational units, especially the Data Coordinating Centers, to introduce the concepts of quality assurance, both new to our collaborators, and stressing the requirements placed on creating a cohort, searching for addresses and contacting cohort members, offering them participation in the project. We made a commitment early in this operation: devote all energies to the search for subjects, screen to detect and diagnose abnormalities in their thyroids and arrange for the follow up care providing detailed documentation for all actions. Treatment and actual follow up operations became the responsibilities of each country's Ministries of Health. Our counterparts in Belarus and Ukraine provided staff, facilities and governmental support such as the relief from customs and duties, salaries for their staff and general oversight of the activities. This still was not without some problems: in Belarus we are working now with the fourth Institute director and the fourth Project Director; there were considerable staff changes and at this time there is only one member left still working with us from the original Belarusian working group; there were three ministers of Health to deal with and even the name of the Institute was changed to bring it into alignment with our field of studies. In Ukraine the directorship of the organizations we deal with remains stable, but there were five ministers of Health appointed during our interaction with local authorities (as well as three U.S. ambassadors). New laws were passed taxing various imports and an Agency for Development and Reconstruction was established in Ukraine with the

sole job of monitoring adherence to these taxation and customs regulations. We developed a working rapport with the higher organizations, but in both countries the local customs officers created the insurmountable problems leading to long delays in delivery of the goods purchased by us for the projects.

Before starting any active collaboration the protocols for each study had to be scientifically peer reviewed and approved by NCI Institutional Review Board and NIH Office for Protection of Research Risks as well as by seemingly comparable Institutional Review Boards in Belarus and Ukraine. Another supervisory body proposed for the oversight of this operation but not yet enacted is the Binational Advisory Group consisting of five members from the USA and each of the collaborating countries.

U.S.A.  
(Serving on both Belarus and Ukraine Groups)

David Becker, M.D.  
Fred A. Mettler, Jr., M.D.  
Bruce Napier  
Roy E. Shore, Ph.D.  
Carole Spencer, Ph.D., M. T.

Belarus

Chistenko, G. N. - Epidemiology  
Markvarde, M. M. - Rad. Diagnosis  
Milyutin, G. Yu. - Radiobiology  
Radyuk, K. A. - Endocrinology  
Tarutin, G. Yu. - Oncology

Ukraine

Bodnar, O. N., Endocrinology  
Frolkis, V. V., Academician  
Korkushko, O. V., Pathophysiol.  
Porevovnikov, O. N. Rad. Dosimetry  
Prisyazhniuk, A. Ye. Epidemiology

These Groups will have the oversight responsibility over both thyroid projects. Leukemia is presently still in the pilot phase. If and when it will develop into a full-fledged study, a similar oversight group will be formed.